TIME-DOMAIN SYSTEM IDENTIFICATION APPLIED TO NON-INVASIVE DETERMINATION OF CARDIO-PULMONARY QUANTITIES

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By

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SUMMARY

This thesis describes an application of the techniques of modelling and time-domain system identification to the processes of respiratory and inert gas transport in the human body. In particular, attention has been focussed on a new non-invasive method for measurement of the total blood flow through the lungs (the cardiac output in normal subjects). Determination of this quantity provides important clinical information on the state of the cardio-vascular system.

This work, being essentially multi-disciplinary, has involved close collaboration with medical personnel - in this case at the Centre for Respiratory Investigation, Glasgow Royal Infirmary. At this establishment much of the development of the homogeneous gas exchange model and practical experimentation have been carried out. The author has principally been concerned with the identification and accuracy aspects of the method.

The starting point of the work involved the examination, in a general way, of data obtained prior to the author's full involvement in the project, which had produced results inferior in terms of reproducibility to that anticipated on the basis of use of a mathematical technique (see Chapter 3).

At this stage, the author became convinced that the route to the solution of the troubles in the technique lay in viewing the problem as one in Statistical Time-Domain Identification. This represented a radical change in approach to the work since previously the model/data comparison and experimental design had been conceived in an 'ad hoc' manner and the identifi ability and accuracy implications poorly understood. Consequently, (in Chapter 4), the original data was viewed in this new light and certain deficiencies of the estimation method were made apparent by posing the problem in this probabilistic context.

The analysis indicated that the cause of the disappointing results was the poor information content of the data rather than the nature of the model itself. This suggested that a better form of experiment be sought. This necessitated study of the area of optimal test signal design to maximise the amount of information encumbent in the resultant data.

Utilising these concepts a new longer form of experiment, aimed at having better properties in respect of cardiac output estimates, was evolved. This work is reported in Chapter 7 where the results of a comprehensive set of reproducibility studies to test the new form of experiment are also presented. These results showed a marked improvement in the reproducibility of the technique, as was exemplified by the fact that the average reproducibility of the cardiac output estimates was 6.2% (4.6% if two rogue results are ignored), as opposed to 12.2% for the earlier studies. What is even more encouraging is that this figure even stands comparison with the average reproducibility of the earlier dye dilution estimates calculated at 6.8% and much of the published results for both invasive and non-invasive methods in the literature.

In Chapter 8 the scope of the work is extended somewhat and here inhomogeneous gas transport models (applicable to diseased lungs) are considered. The concept of designing identification methods to optimally discriminate between these models and homogeneous models is tentatively introduced as a mechanism for quantitative diagnosis of lung dysfunction and some prefatory simulation work in this vein presented. A technique crucial to the mechanisation of the identification methods underlying much of the work detailed in this thesis is that of Function Minimisation. A large proportion of the time allocated for this Ph.D. project was spent on the investigation of recent, numerically stable computer algorithms for this purpose.

Chapter 5 investigates the usefulness of generalised descent methods in the context of the particular application for this project, whilst Chapter 6 is devoted specifically to methods for sums of squares problems. A technique due to Gill and Murray (124) is shown to be superior to all others for estimating the parameters of the lung model and thus this algorithm is used to generate the results subsequently presented in the rest of the thesis.

When creating the software for the Function Minimisation, great care was taken to configure it in a general manner. This philosophy thus led to the creation of a flexible Function Minimisation package as a useful by-product of this work at very little extra programming effort. This the author feels constitutes a piece of software which could be of general use in a wide number of different applications. Details of this package are outlined in Appendix B.

DEDICATION

This thesis is dedicated to two people, my wife Anne and my late father Richard Bache. The former has assisted me morally, financially and practically throughout the period of this research. The latter has had great influence on the path of my life and, in particular, has been instrumental in inclining me towards academic pursuits of which this dissertation is the culmination.

ACKNOWLEDGEMENTS

This thesis describes research carried out during the period September 1976 to October 1979 under the supervision of Professor J. Lamb, James Watt Professor of Electrical Engineering and Dr. D.J. Murray-Smith, Senior Lecturer, both of the Department of Electronics and Electrical Engineering, University of Glasgow.

The work was carried out at the above Department and also for periods at the Centre for Respiratory Investigation, Glasgow Royal Infirmary. I would like to thank Professor Lamb for the provision of research facilities within his Department and Dr. F. Moran, Consultant Physician, for similar discretions at C.R.I. Financial support by the Science Research Council is also gratefully acknowledged.

It is ridiculous to think that a task of the nature addressed in this thesis could be accomplished alone; an interdisciplinary research project is, inevitably, collaborative. I have been particularly fortunate in having extremely good colleagues in this work. In this respect I am particularly indebted to Bill Gray, my major collaborator at C.R.I., and Dave Murray-Smith, my supervisor, for their continued advice and constructive criticism through this project. Thanks are also due to Allan Pack and other past and present clinical staff of the C.R.I. for many helpful discussions. Ian Logan, Linda McCormick and David Findlay also provided useful computational assistance at various stages of the work.

I should finally like to thank Miss Brenda Caldwell for the skill and patience she exercised in typing this thesis.

CONTENTS

CHAPTER I

INTRODUCTION

1.1 General Introduction

This dissertation is an account of how a technique familiar to the modern control engineer (i.e. System Identification) was applied to an unusual problem - the indirect measurement of the parameters of the human respiratory gas exchanging system. Of the parameters of this system, one in particular has considerable clinical significance. That is the pulmonary blood flow parameter which, in normal subjects, is synonymous with the cardiac output. Traditional clinical methods of measuring this quantity in humans are invasive, which is obviously undesirable.

The work described in this thesis in fact forms only part of a larger project, which has been a basis for collaboration between the Control Group, Department of Electronics and Electrical Engineering, University of Glasgow, and the Centre for Respiratory Investigation, Glasgow Royal Infirmary. This broader study is concerned with the investigation of dynamic mathematical models in the context of respiratory medicine and their possible uses as diagnostic aids. Conventional tests of pulmonary function (72) have been based largely on mathematical descriptions of respiratory gas transport which are valid only in the steady-state. Such conditions may be difficult to establish in practice, particularly in ill, irregularly breathing subjects. Clearly, dynamic models are necessary in such situations.

In the course of this broad investigation, a dynamic homogeneous CO_2 gas transport model has been developed and the concept of using this as a tool to indirectly infer the numerical values of associated cardio-pulmonary parameters of real subjects has evolved. This is the area of the overall research work with which this thesis is principally concerned.

Prior to the involvement of the author in this project, some preliminary

development work and identification experiments had been carried out to validate the proposed new method with limited success (234,228). Although the results were satisfactory as regards overall accuracy, in terms of repeatability they were rather poor. Thus, this Ph.D. project was commissioned to investigate the identification aspects of the technique in a more rigorous way than done hitherto. The primary aim of the research was to uncover mechanisms to increase the reproducibility of the cardiac output estimates obtained from the non-invasive measurement method. The major part of this thesis serves to document the progress which has been made towards this end by the author over the last three years. There is always benefit to be gained, however, from addressing the general rather than the specific where this can be done. Thus, the purpose of this first chapter is to outline the ideas and highlight the difficulties involved in modelling and identification of biological systems generally. It also introduces some concepts upon which much of the work in succeeding chapters is based.

1.2 Mathematical Modelling of Biological Systems - Personal Perspective

In science, the notion of modelling is one of central importance in solving problems concerned with the real world. Indeed, this has been so since the 16th century when Galileo, for the first time, answered questions concerning reality by analysis of an abstraction of reality - a model. Prior to this time, natural events had been explained teleologically.

What precisely is a model ? For our purposes the definition in Eykhoff (97) suffices. That is "a model is a representation of the essential aspects of an existing system (or system to be constructed) which presents knowledge of that system in usable form." It is interesting that explicit in this

definition is the statement that the model is a representation of some aspect of the system rather than the system as a whole, thus implying that no model can hope to completely define any given system. This in turn implies that the aspect of the system to be modelled is 'separable' (168) from its causal environment. In fact this latter conclusion is not trivial and it is one of the basic axioms of modelling that this can be done.

At precisely what level of detail this conceptual line between model and environment should be drawn is a difficult question. That is, although it is desirable to use the model most isomorphic with the real system, it is also equally obvious that such a model will be inevitably more complex, and as a consequence, perhaps less cost beneficial than a less realistic but simpler model. Thus, in practice, a balance has to be struck between the desirable isomorphism of the model and the complexity of the model which can be handled. Such a model is termed a parsimonious model (39).

Historically, the idea of a model differs in the quantitative sciences as opposed to the more descriptive biological sciences; the level of abstraction of reality being higher in the former than in the latter. For example, in engineering use is commonly made of mathematical models whilst in medicine conceptual or phenomenological models are most often encountered. This imbalance has been partially corrected over the last twenty years, however, with analytical description of biomedical systems (and especially physiological processes) becoming increasingly popular over this period. The proliferation of recent texts on the subject attests to this (142,210, 244).

Mathematical models of man-made systems are used for a wide variety of purposes which can be broadly categorised as follows :-

(i) to gain insight (48),

(ii) to forecast (39),

(iii) to control (10, 226),

(iv) to assist in taking decisions (37, 266).

In contrast to this, the purpose of the modelling exercise in the biological field has tended to be less clearly defined. For many physiologists and clinicians, struggling with differential and integral equations seems to have become an end within itself. Take, for example, the mathematical modelling activity in the study of respiratory control. Modelling of this particular physiological system has attracted much attention in the literature ever since the seminal paper of Grodins et al (143) in 1954. The major function of the models developed in this area so far (many of these are reviewed in (303)), seems to have been to provide a convenient, functional, systems summary of current conventional wisdom. However, since all these models serve to do is emphasise the sufficiency of one particular explanation, they thus contribute little to furthering understanding of respiratory regulation and control, which surely should be the main object of the modelling exercise in such work. It seems obvious that only by promoting confrontation among competing models can real insight be generated, yet only comparatively recently have such tactics been employed in this area (275).

Generalising again, this preoccupation on the part of the bio-mathematicians with modelling as a "raison d'etre" is an unfortunate aspect of the biological systems literature and is perhaps a reflection of the relative infancy of the field. However, this represents a fairly trivial utilisation of the power of simulation and it is time this tendency was outgrown. It is the tenet of this study that only when attention is directed to really <u>using</u> these biological process models for a clearly defined purpose will positive benefit be gained,

especially in the biomedical area.

In the opinion of the author there are three applications areas particularly deserving of attention in the above respect.

(i) The use of mathematical models for indirect measurement of physiological quantities.

(ii) The use of mathematical models for testing various hypotheses concerning the true nature of a biological system under test.

(iii) The use of mathematical models to aid control (i.e. treatment) of diseased biological systems.

In this thesis attention is focussed on applications (i) and (ii) in the specific context of the human respiratory gas transport system. To practising clinicians, as opposed to researchers, however, application (iii) is likely that of most interest in terms of the ultimate benefits they see accrueing. Unfortunately, to date, reported instances of "closing of the biological loop" have been few in number (262). This is largely attributable to the following.

In order to apply control synthesis techniques in the biomedical area, numerical values of the system model parameters must be readily available. These will be strongly subject dependent and hence it will be necessary to measure them in each patient to whom it is intended to apply the eventual control scheme. That is, indirect measurement of the model parameters will be a necessary prerider to control. Therefore, ethically clinicians have been unwilling to condone use of models for control whilst in their eyes credibility has yet to be established for the use of mathematical models for indirect measurement in this area. Thus, in the opinion of the author success in the latter area is the basic building block on which success in the former will be founded. This, in a sense, forms a further justification for the work to be

subsequently described in this thesis.

1.3 System Identification in Biological Systems

This problem of indirect measurement of internal quantities in mathematical models, as referred to in the previous section of this Chapter, is also of considerable interest in engineering circles. Here a new discipline has evolved which provides tools to allow this information to be extracted from experimentally observed input-output data for the system under investigation. This discipline is known as System Identification.

As far as "modern" control engineers are concerned, system identification has its roots in the early analysis methods used in "classical" control theory to design control strategies from frequency response measurements. However, the statistician might argue that, in the time-domain at least, system identification can be looked upon as simply an extension of the regression analysis techniques of statistical inference to admit the class of dynamic models. Zadeh (306) defined identification as "the determination on the basis of input and output, of a model within a specified class of models, to which the system under test is equivalent"; equivalence being defined in the context of the particular identification method being used.

In the time-domain, there are basically two approaches to the problem. The choice of which to use in a given situation is directly dependent on the ultimate use to which the model is intended to be put. In the first approach, no prior system knowledge is assumed. This is the celebrated "black box" or "total ignorance" identification problem (24). Here a model of quite general structure is identified which defines an empirical relationship between the observed system's inputs and outputs. This relationship may have no physical significance other than that it is experimentally true. Such a model is called a functional model (272) and may be perfectly satisfactory where only

the external behaviour of the system under study (i.e. the input/output behaviour) is of concern e.g. for control purposes. However, in the case where the internal system interactions are of interest and/or there is a priori structural knowledge, as in the application detailed in this thesis, such an approach may not be appropriate. This later situation corresponds to the so-called "grey-box" identification problem (24). In this approach the structure of the model is deduced from the application of basic physical laws (e.g. Kirchoff's Laws, conservation of mass, etc.) and only the coefficients appearing in the resultant ordinary or partial differential / difference equations remain to be identified. This type of mathematical model is variously termed a structural (272) or mechanistic (39) model since the parameters appearing in the model equations generally have intrinsic physical significance.

Often in the literature the term "identification" has the connotation of the investigator possessing no a priori physical insight into the problem. Thus, in the latter case discussed above, i.e. the "grey box" problem, which clearly does not correspond to this, the usage parameter estimation is frequent, especially to the statisticians who originated the term. In this thesis, however, engineering loyalties will be upheld by taking the term identification to refer to both the "black" and "grey" box problem and will frequently use the terms identification and parameter estimation interchangably in the latter case.

As discussed in Section 1.2, although the use of mathematical models is becoming widely accepted in the biological community, system identification has had a less enthusiastic reception. Some reasons behind this scepticism are as follows (27).

(i) There is an ingrained preference on the part of biological investigators for measurements which are obtained directly (i.e. in the laboratory) and a corresponding suspicion of those deduced in a less tangible fashion.

(ii) There is difficulty in applying identification techniques due to the inherent variability and non-linearity of biological systems.

(iii) Homeostasis in living organisms makes separability (168) difficult and hence inputs and outputs of biological systems are difficult to isolate. This frequently leads to parameter estimates which are not unique and therefore of dubious value.

Despite these barriers the battle for credibility for system identification techniques applied to biological systems continues. Some applications reported in the literature will now be reviewed.

The most widely used models of biological systems make use of the notion of a compartment. A compartment can be viewed as a homogeneous entity representing several elements of the one type of organism lumped together. Systems which can be modelled in this compartmental or lumped parameter manner are particularly suitable for the application of identification techniques since the equations which result from this approach are ordinary rather than partial differential equations. For this reason the various subsystems concerned with mammalian respiration, which are of this type, have attracted considerable attention as regards identification. In (128, 129) an application of parameter estimation to a non-linear lumped parameter model of pulmonary airway dynamics is described and the clinical significance of this technique discussed in relation to chronic obstructive airways disease. Similar work in this area is that of Peslin et al (236) (who use a frequency-domain approach) and Feinberg and Schoeffer (106). These latter authors also address the problem of Function Minimisation which is an important part of the Time-Domain System Identification problem. This topic is also extensively discussed in Chapters 5 and 6 of this thesis in connection with estimation of the parameters of the gas exchange model.

The dicussion of identification techniques applied to lung gas exchange models, which have been reported in the literature, is more properly reserved to Chapter 3 of this thesis.

Stoll and Meditch (268) have applied a least squares identification technique to the human respiratory control system itself. In the study of this system (in humans at least) separability becomes a problem since the lung-trachea gas transport system is interposed between the true input to the respiratory control system (gas concentration in the lungs) and the only input which can be ethically applied in practice (gas concentration at the mouth). Swanson et al (277, 278) have evolved a novel technique to circumvent this difficulty termed "dynamic end-tidal forcing". Basically this consists of using a predictive type of chamber gas concentration input to anticipate the lung-trachea dynamics and manufacture the desired input response within the lungs themselves. This system has been used in subsequent identification studies to give insight into the quantitative aspects of the regulation of respiration (276, 279, 274, 29, 280, 296) and to identify the site of action of drugs (169). The work of this group, and in particular Swanson's thesis (272), represents an important contribution to the biological identification literature since it emphasises for the first time in this area, the importance of experiment design on the subsequent accuracy of identification (273) and its role in model discrimination (275). Also, it is conspicuous in the field by its use latterly (29, 280, 296) of some fairly advanced time-domain system identification methods. In this respect, this work has had a large effect on that described in this present thesis.

Identification techniques have also been applied to the study of the mammalian muscle reflex control system (199, 202, 195, 196, 160). Most of the applications of system identification techniques in biology, however, have been in the area of tracer kinetics. (This latter term is a broad brush one to

cover the investigation of the kinetics of such things as drugs, enzymes, chemical reactions, pharmological agents, etc. "in vivo" by tracer techniques.) Kinetic modelling, as such, is not new. Graphical methods, e.g. the "peeling" method (259) have been used to fit exponential tracer test data to sums of exponentials for some years now. In recent times more computing power has been applied (180, 198) to make the process more efficient. However, these methods are still essentially "black-box". Under the influence of engineers, modelling and identification procedures are beginning to be applied in this area, which are based more on a priori knowledge rather than simply observational data. This is especially true in the context of metabolic systems. For example, Wilson et al (298) and laterally Distefano et al (89) have considered the identification of a compartmental model of thyroid hormone metabolism. Brown and Godfrey (49) and Cobelli et al (66) have investigated bilirubin kinetics by identification methods. This new approach leads to a better understanding of the underlying physiological process and/or helps devise experimental conditions, which aid diagnosis of diseased states (208, 211).

In such complicated metabolic models careful attention must be paid to possible non-uniqueness of the resultant parameter estimates and, in fact, a large part of the literature in this area addresses this very question. This important topic will be more fully discussed in Chapter 4. The problems associated with applying identification techniques to metabolic systems are discussed in a more general sense by Carson and Finklestein (55) and more recently, in the review by Carson et al (56). Further applications of system identification to all the systems mentioned above, and in addition to the cardio-vascular, nervous, visual and human operator systems, can be found in the comprehensive survey papers by Bekey (25) and Bekey and Beneken (26).

The majority of identification applications cited in the biological literature so far have been off-line methods. In concluding this section it is perhaps worth noting that, in the industrial process control field, over the last decade the emphasis has gradually shifted away from the design philosophy of off-line identification and subsequent fixed controller design, towards one of simultaneous on-line identification and control. Attention has especially been focussed on the so-called "self-tuning regulator" (15, 64,293), a simplified form of stochastic adaptive controller which ignores the complicating interaction between identification and control (21). It is the opinion of the author that the biological area represents an ideal vehicle for application of these techniques and, speculating into the future, believes that progress in this respect will ultimately mirror that currently being made in industrial process control.

1.4 General Considerations in System Identification

As discussed in the previous section, most models of biological systems utilise the concept of the compartment. Such compartmental systems may be best represented mathematically in a state-space framework (95). That is, an "n" compartment linear system could be represented by the set of equations

$$\frac{dx}{dt} = A_1 x(t) + B_1 u(t) \qquad 1.1$$

$$y(t) = C x(t) + D u(t) \qquad 1.2$$

where x is an "n" vector, typically representing the concentration of a particular material in each of the "n" compartments, u an "r" vector of inputs input to the compartments and the matrices A_1, B_1, C, D constant matrices, whose elements will be functions of the "physical" parameters β of the system of interest. In the discrete time case, this system can be written as :

$$x(k+1) = A\,x(k) + B\,u(k) \qquad 1.3$$

$$y(k) = C\,x(k) + D\,u(k) \qquad 1.4$$

where $k = 0, 1, 2, \ldots$ etc., the matrices A, B being related to A_1, B_1 by familiar equations (156).

As is well known in the systems literature, there is some redundancy in these representations as regards input-output relations (95) and in fact the coefficients of the matrix quadruple (A, B, C, D) can be parameterised in terms of the inherent "physical" model parameters in many different ways. This can be advantageous. That is, in many situations where the "natural" parameterisation is not convenient for identification purposes it is frequently possible to exploit this redundancy to obtain a better representation. For example, a canonical form in the multi-input, single-output case for equations 1.3 / 1.4 with $D = 0$ is obtained by employing a suitable equivalence transformation so that A becomes a matrix of companion form (156).

$$x(k+1) \begin{bmatrix} -a_1 & 1 & \cdots & 0 \\ -a_2 & 0 & 1 & 0 \\ \vdots & \vdots & \ddots & \vdots \\ -a_{n-1} & \vdots & & 1 \\ -a_n & 0 & 0 & \cdots\ 0 \end{bmatrix} x(k) + \begin{bmatrix} b_{11} & \cdots & b_{ir} \\ b_{21} & & \vdots \\ \vdots & & \vdots \\ b_{n1} & & b_{nr} \end{bmatrix} u(k) \qquad 1.5$$

$$y(k) = \begin{bmatrix} 1 & 0 & 0 & 0 \end{bmatrix} x(k) \qquad 1.6$$

By eliminating the state variable x we obtain the following input-output relation.

$$y(k) = a_1 y(k-1) + \ldots a_n\, y(k-n) + b_{11}\, u_1(k-1) + \ldots b_{n1}\, u(k-m) + \ldots b_{ir}\, u_r(k-1) + \ldots\ldots + b_{nr}\, u_r(k-n) \qquad 1.7$$

The equation can be written in slightly more compact form as

$$y(k) = \frac{B(z)}{A(z)} \quad u(k) \qquad 1.8$$

where z is the shift operator defined by

$$z\,x(k) = x(k+1) \qquad 1.9$$

and A a polynomial, B a polynomial matrix in this operator defined by

$$A(z) = z^{n} + a_1 z^{n-1} + \ldots\ldots + a_n \qquad 1.10$$

$$B(z) = \left[b_{11} \ldots b_{1r}\right] z^{n-1} + \ldots + \left[b_{n1} \ldots b_{nr}\right] \qquad 1.11$$

This representation is well-known to the industrial process control identification community (13). Its special structure is such that it is linear in its parameters ($a_1, \ldots a_n, b_{11}, \ldots b_{1r}, \ldots b_{n1}, \ldots b_{nr}$). A model is characterised as being linear in its parameters if the model output is a linear function of each model parameter. That is the model can be written in the form

$$Y = X\,\beta \qquad 1.12$$

where the elements of the so-called sensitivity matrix X do not depend on β (22). In identification use of a mathematical model which is linear in the parameters leads to an estimation problem which admits a closed form solution. On the other hand, use of a model which is non-linear in the parameters leads to a problem which can only be solved by iterative methods. This will be further explained in Chapter 4. Suffice it to say, however, at the moment, that the importance of using models linear in the parameters in time-domain biological system identification, where this can be accomplished, cannot be over-emphasised.

Having chosen a model structure whose parameters can be determined from input-output relations, or in the terminology of (191) a class of models $\{M\}$ it then remains to find the parameters of the model, that is one model in the specified class $\{M\}$ which fits the experimental data. The choice of a

a criterion function by means of which the "goodness of fit" of the model responses to the actual system responses can be evaluated is crucial in this respect.

Ideally, a cost function would be some distance measure between the parameter estimates $\hat{\beta}$ and the true parameter vector β . Of course, the problem with this is the true parameter values are not known a priori. Therefore, it is more common for the comparison to be based on some distance measure of the error between the system and model responses, e.g. the output error (13) or some form of more generalised error dependent on both input and output (13). The actual criterion function used can be chosen "ad hoc" as is done in Chapter 3 of this thesis. However, as we shall see in Chapter 4, the criterion function used is implicitly related to the nature of the disturbances corrupting the measurements and it is possible to gain some advantage by giving a statistical interpretation to a criterion. In fact, a major difficulty in mathematical modelling of biological systems is how to handle uncertainty, i.e. in many problems the characteristics of the disturbances can be as important as the system dynamics. During the post-war development period control engineers were beginning to be faced with similar problems in their field. For example, the deterministic control theory of the period only took disturbances into account in a heuristic manner and hence had difficulty in recognising the explicit difference which exists between an open-loop control strategy and an "equivalent" closed loop one. However, under the influence of such names as Wiener and Kolmogorov, a new discipline was evolved to handle such problems; stochastic control theory (9). Central to this new theory was the concept that disturbances could be modelled as stochastic processes (9).

For most problems of scientific interest, it transpires that this approach amounts to the disturbances being simulated as the output of a linear

filter driven by white noise. In Chapter 4 of this thesis it will be shown how such a functional "noise model" can be combined with the structural gas exchange model derived from physical principles to give a better representation of the biological system under study.

CHAPTER 2

HOMOGENEOUS MODELS OF THE HUMAN GAS TRANSPORT PROCESSES

2.1 Introduction

External respiration is the carriage of respiratory gases (O_2 , CO_2) between the atmosphere and the tissues of the body. The need for such a process arises from the nature of human metabolism.

Man requires energy whether at work, exercise, or even whilst asleep. This energy is mainly derived from the oxidation of foodstuffs. Also, the main end-product of this reaction is carbon dioxide. Thus, the tissues are continually demanding oxygen and producing carbon dioxide.

This uptake and excretion will not be constant, but will vary with energy requirements. Thus, there is a functional requirement for a regulatory mechanism to maintain the levels of these gases in the tissues within reasonable limits for homeostatic purposes. This regulatory mechanism is known as the respiratory control system. It controls gas levels in the respiratory "plant" or controlled system primarily by manipulating the ventilation of the lungs. As discussed in the previous chapter, this system has already been subject to a great deal of mathematical treatment. However, in this thesis the modelling effort will be concerned, not with the control system itself, but rather the controlled plant, i.e. the human gas transport system.

Conceptually, the human gas transport system can be thought of as being made up of two constituent parts.

(1) The system responsible for carriage of respiratory gases in the air phase, i.e. that which transports gases from the external environment to the alveolar membrane and vice versa.

(2) The system responsible for carriage of respiratory gases in the liquid phase, i.e. that which transports gases from the pulmonary capillaries to the tissues and vice versa.

Anatomically, sub system (1) consists of a series of bifurcating tubes, i.e. beginning with the trachea (or windpipe), dividing into the two bronchi and each of these major airways diving 23 more times and eventually terminating in tiny sacs called alveoli, where gas exchange takes place with the blood. The earlier generation airways (i.e. the upper airways) do not take part in gas exchange to any extent, although they are still ventilated. This ventilated region constitutes "wasted ventilation" and for this reason this gas volume is known as the "anatomical dead space".

In sub system (2) there is branching between the pulmonary artery and the pulmonary vein, eventually terminating in the pulmonary capillaries which are in direct contact with the alveoli.

It is across this gas-blood interface (alveolar membrane - pulmonary capillary wall) that gas exchange takes place. Despite the small size of the lungs, due to the bifurcating structure, the interface area is very large (70 - 100 m^2), which facilitates efficient gas exchange. Although gas is transported to the gas-blood interface mainly by convection (bulk flow) gas transfer across this membrane itself takes place largely on the basis of partial pressure gradients. Thus, pulmonary arterial (venous mixed) blood comes into the lungs from the tissues high in CO_2 and low in O_2 . In contrast, alveolar air is nearer the gas partial pressure levels of the external environment which is high in O_2 and low in CO_2 . Therefore, due to the partial pressure gradient there is a net transfer of O_2 from the lungs to the blood and of CO_2 from the blood to the lungs. Thus, the pulmonary venous (arterial) blood leaves the lungs high in O_2 and low in CO_2 and goes to the tissues where net gas transfer takes place in the opposite direction to that in the lungs since here the partial pressure gradients are reversed.

In the human gas transport system four areas for modelling attention will be identified, which will be pursued at various places in this chapter.

(1) Modelling of convective (perhaps diffusive) gas transport between the external environment and the alveolar regions.

(2) Modelling of alveolar membrane/pulmonary capillary gas exchange.

(3) Modelling of the relationship between partial pressure (gas tension) and content in the blood in situations where this is not a porportional relationship (i.e. the gases used do not obey Henry's Law). This will be especially important for the respiratory gases O_2 and CO_2, which combine chemically with the blood.

(4) Modelling of the arterial blood to venous blood "tissue loop" and inherent transport delays.

Several simplifying assumptions are required to keep the analysis of these sub-systems within reasonable bounds. However, perhaps the most important refers to modelling area (2) and this will be discussed below.

To keep the order of the resultant differential equations involved low, it is useful to assume that the lungs are'homogeneous', i.e. all the alveoli on the gas side and all the pulmonary capillaries on the blood side can each be lumped into one structure (that is single numerical values can be assigned to the partial pressures in all the alveoli and in all the pulmonary capillaries). This assumption is perfectly adequate to describe normal lungs (and is almost universal in classical respiratory physiology), but will have the effect of invalidating the model in the presence of significant abnormalities or inhomogeneities such as exist in disease. Inhomogeneous models are discussed in Chapter 8.

2.2 Mathematical Concepts and Quantities in Human Gas Transport

Before going on to undertake modelling of human respiratory gas exchange, familiarisation with the standard units and symbols used in this area is necessary.

In the early days workers in gas exchange physiology were short on ideals of interchange and co-ordination and the resultant mathematical language used reflected this disharmony. However, the 1950 Atlantic City standardisation (232) introduced clarity into the field and has served to unify gas exchange modelling with respect to units and symbols until very recently. This 1950 standard system of units and symbols is used in this thesis and is outlined in Table 2.1 below. The basic concept behind the system of units is that amount of gas, i.e. quantity of substance, be represented by a volume expressed at a set condition of temperature and pressure - conventionally BTPS (Body Temperature and Pressure Saturated (with water vapour)). [In 1971 Piiper et al (238) suggested the alternative concept where amount of gas was expressed in moles. However, although this has certain advantages, it has not as yet become universally popular with physiologists who still seem to prefer the 1950 system. For this reason the "new" system has not been used in this thesis.]

Concentration in the air phase in our system of units is represented by the dimensionless quantity fractional concentration F (volume of gas species under consideration/volume of gas medium). The relationship between fractional concentration and partial pressure is described simply by Dalton's Law, i.e.

$$P_x = F_x P \qquad 2.1$$

where F_x is fractional concentration of a gas species x , P_x the partial

Quantity	Symbol	Units
Partial Pressure	P	mm.Hg (Torr) or kilopascal (KPa)
Volume of gas (gas in air phase)	V	Litre (at BTPS)
Fractional concentration (gas in air phase)	F	Dimensionless
Volume flow rate	$\dot{V}$	Litre/min
Conc. of gas in liquid phase	C	ml. of gas at STPD/ 100 ml liquid
Solubility in blood (for gases which obey Henry's Law) Bunsen solubility coefficient	α	Vol. of gas at STPD/ Vol. of liquid/ atmosphere of pressure.
Ostwald solubility coefficient	α'	Vol. of gas at BTPD/Vol. of liquid/atmosphere of pressure $\alpha' = \alpha \times 1.163$

SUBSCRIPTS	
Upper Case Letters (for gas phase)	Lower Case Letters (for blood phase)
I Inspired	a arterial
E Expired	$\bar{v}$ mixed venous
$\bar{E}$ Mean end expiratory	
A Alveolar	

TABLE 2.1 : Standard Symbols from Atlantic City Standardisation

pressure and P the total gas pressure. Relationships concerning the carriage of a gas in a liquid may be developed by invoking the concept of gas tension. This is defined as that partial pressure of a gas species x in a gas mixture which, if exposed to the liquid, would not result in any net exchange of x . Thus, saying a gas and liquid mixture are equilibrated is synonymous with saying the partial pressures of the component gas species are identical in the gas and liquid media. The tension of a gas in a liquid, as defined above, is related to concentration.

For gases which dissolve in the liquid, Henry's law tells us this concentration - partial pressure relationship is a matter of simple proportionality. We shall call such gases in the context on this thesis inert gases, inert in the biological sense as first defined by Kety (173). Since, in the 1950 system of units, quantity of gas in the liquid is expressed as a volume at STPD, it is usual to use the Bunsen solubility coefficient as the constant of proportionality in the linear concentration - partial pressure relationship. Thus, we have

$$C_x = \alpha_x \frac{P_x}{P} \qquad 2.2$$

where C_x is the concentration of gas species x in the liquid, P_x its partial pressure α_x the value of the Bunsen solubility coefficient for x and P the total pressure.

Sometimes, especially when equating uptake in the liquid phase with output from the gas phase, it is more convenient with inert gases to use the Ostwald solubility coefficient in equation 2.2, as this obviates manipulations involved in considering volumes of gas in the air phase at BTPS and in the liquid phase at STPD. For the important respiratory gases O_2 and CO_2 unlike inert gases, there is no simple relationship between tension and concentration in the liquid phase, since these gases combine chemically with the blood and hence the resultant

content - partial pressure relationships are non-linear. These nonlinearities (i.e. Haldane effect for CO_2 , Bohr Shift for O_2) lead to an increase in efficiency as regards gas exchange, but complicate mathematical treatment. These two special cases will be treated in Section 2.3. Using the units and symbols introduced above, basic equations of gas exchange in the lung may be derived by the simple application of the principle of conservation of mass. For example, the uptake of a gas x from the external environment to the lung may be derived as :

$$\dot{V}_x = \dot{V}_I F_{I_x} - \dot{V}_E F_{E_x} \qquad 2.3$$

Uptake (Vol. BTPS/ unit time)	Amount Inspired	Amount Expired

In breathing normal respiratory gas mixtures $\dot{V}_I$ does not normally equal $\dot{V}_E$ since more oxygen is taken up than CO_2 produced. (i.e. the respiratory gas exchange ratio $\frac{\dot{V}CO_2}{\dot{V}O_2} < 1$). An expression describing the uptake of a gas x from the blood to the lungs may also be written as :

$$\dot{V}_x = \dot{Q} (C_{\bar{v}x} - C_{ax}) \qquad 2.4$$

Uptake (Vol. STPD/ unit time)	Net transfer from blood

Equation 2.4 is known as the Fick equation and equating equations 2.3 and 2.4 is the basis of the various methods of measurement of cardiac output which will be discussed in the succeeding chapter.

When equating gas uptake from the environment with transfer to the blood, quantities in the above equations must be expressed at the same conditions of temperature and pressure and, therefore, use of a correction

factor is necessary, i.e.

$$\dot{V}_{x\ (STPD)} = k\ \dot{V}_{x\ (BTPS)} \qquad 2.5$$

where k is the reduction factor from BTPS to STPD conditions given by

$$k = \frac{(B - 47)}{B} \cdot \frac{273}{310} \qquad 2.6$$

B in this case being the barometric pressure in mm. Hg.

2.3 Concentration - Partial Pressure Relationship for O_2

Oxygen is carried in blood mainly in chemical combination with a substance called haemoglobin, a protein found in the red blood cells (erythrocytes).

$$O_2 + Hb \rightleftharpoons Hb\,O_2 \qquad 2.7$$

Oxygen	(reduced) haemoglobin	Oxyhaemoglobin

This is a reversible reaction. Just to what side this reaction is biased depends mainly on the partial pressure of O_2 in the immediate environment, i.e. the reaction is biased to the right hand side in alveolar regions (high PO_2) to allow uptake of O_2, but to the left in the tissues (low PO_2) to elicit unloading of O_2 from oxyhaemoglobin.

The curve relating percentage saturation of the O_2 carrying power of haemoglobin (maximum O_2 that can be carried by one gram of Hb is approximately 1.39 ml) to PO_2 is known as the oxyhaemoglobin dissociation curve. This has the characteristic sigmoid shape which is shown in Fig. 2.1.

The reaction above is also dependent to a lesser extent on temperature, acid-base status (pH) of the blood and CO_2 partial pressure (the Bohr effect).

THE O_2 DISSOCIATION CURVE

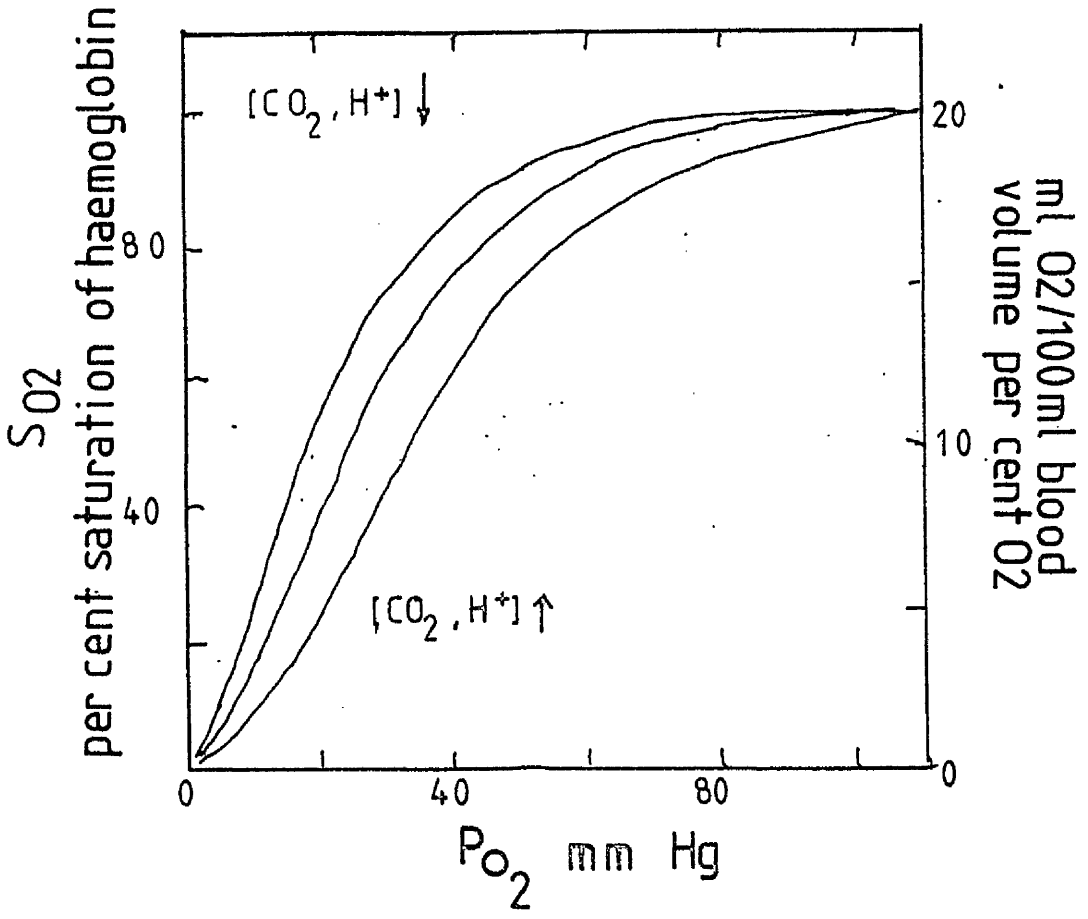


FIGURE 2·1

The latter effect causes the Hb O_2 dissociation curve to shift to the right with increasing PCO_2. This is advantageous, e.g. where an increase in CO_2 partial pressure locally during tissue activity would cause HbO_2 to part more readily with its O_2 to the active tissues. A certain amount of O_2 is also carried in direct solution in plasma. This, however, is a lot less than that carried combined with haemoglobin since the Bunsen solubility coefficient of oxygen in blood plasma is small ($\alpha_{O_2} \approx 0.3 \times 10^{-4}$). Thus the concentration-partial pressure relationship can be written in terms of these two distinct components as follows :

$$CO_2 = f(PO_2) = Cap. \frac{S(PO_2)}{100} + \frac{\alpha O2}{760} \cdot PO_2 \qquad 2.8$$

where Cap is the product of oxygen capacity of haemoglobin at 100% saturation (1.39 ml/g Hb) and the blood Hb concentration (g Hb/100 ml whole blood), S is the percentage haemoglobin saturation as given by the Hb O_2 dissociation curve and α_{O2} the solubility of oxygen in blood plasma. The first term in the above equation gives the amount of O_2 in chemical combination and the second the amount of O_2 in physical solution. To use the above equation a mathematical expression is also required to describe the dissociation curve in a form for S above as a function of PO_2. Various empirical formulae have been suggested, Visser et al (287) used.

$$S(PO_2) = \left\{ 1 - e^{-(k \times PO_2)} \right\}^2 \qquad 2.9$$

This was based on the curve obtained by Dill and Forbes (85) from the data of Bock et al (34); as is the modified formula of Murphy (212).

$$S(PO_2) = \left\{ (1 - e^{-0.04\, PO2}) \; (1 - e^{-0.08\; PO2}) \right\}^{1.1} \qquad 2.10$$

This data, however, was based on measurements from only one man. Servinghaus (256) has obtained a curve which was averaged from data for ten

adults. The form of dissociation curve eventually used in this thesis is that of Kelman (170) which is based on that of Servinghaus. Kelman's equation is

$$S(PO_2) = \frac{C_1 PO_2 + C_2 PO_2^{\,2} + C_3 PO_2^{\,3} + C_4 PO_2^{\,4}}{C_5 + C_6 PO_2 + C_7 PO_2^{\,2} + C_8 PO_2^{\,3} + C_9 PO_2^{\,4}} \qquad 2.11$$

where C_1 , C_2 ..... , C_9 are constants.

For the work described in this thesis this equation was rearranged in factorised form (which is much more convenient for computation) as

$$S(PO_2) = \frac{100\left[PO_2 \left\{ PO_2 \left(PO_2 \left\langle PO_2 + a_3 \right\rangle + a_2 \right) + a_1 \right\}\right]}{\left[PO_2 \left\{ PO_2 \left(PO_2 \left\langle PO_2 + a_7 \right\rangle + a_6 \right) + a_5 \right\} + a_4\right]} \qquad 2.12$$

where a_1 , a_2 , ... , a_7 are derived directly from Kelman's coefficients and are :-

$$a_1 = -8.532229 \times 10^3 , \quad a_2 = 2.121401 \times 10^3 , \quad a_3 = -6.707399 \times 10^1 ,$$
$$a_4 = 9.359609 \times 10^5 , \quad a_5 = -3.134626 \times 10^4 , \quad a_5 = 2.396167 \times 10^3 ,$$
$$a_7 = -6.710441 \times 10^1 .$$

The Kelman formula (170) was envisaged for given values of PCO_2 (40 mm. Hg), blood pH (7.4) and body temperature (37° C). Correction formulae for the basic equation were given for other values of these various factors. For example, if PCO_2 is <u>not</u> 40 mm Hg, then PO_2 in equation 2.12 is replaced by the following expression

$$PO_2' = PO_2 \times 10^{\left[0.06 \left(\log 40 - \log (PCO_2) \right)\right]} \qquad 2.13$$

However, Ferguson (108) has shown that the effect of these correction factors, even cumulatively, is small ($< 4\%$) over the PO_2 ranges of physiological interest. Thus, these modifications will be ignored in the dynamic O_2 gas exchange model used in this thesis.

2.4 Concentration - Partial Pressure Relationship for CO_2

Despite the fact the solubility of CO_2 in blood is some twenty times greater than O_2 , CO_2 is, like O_2 , transported in the blood in chemically combined form. The bulk of it is carried as bicarbonate. The reaction is summarised below.

$$CO_2 + H_2O \overset{\text{c.a.}}{\rightleftharpoons} H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad 2.14$$

Although this reaction can (and does) take place in plasma, it is chiefly carried out in the red blood cells (erythrocytes), where the presence of the enzyme carbonic anhydrase (c.a.) catalyses the first step of the reaction above.

A large part of this bicarbonate formed in the erythrocytes then dissolves back into the plasma in exchange for the shift of chloride ions in the opposite direction, which maintain electrical neutrality. This reaction is dependent on CO_2 partial pressure and is conveniently driven to the right in the tissues and to the left in the alveoli.

Not all CO_2 is transported as bicarbonate; some is transported as carbamino bound CO_2 ; largely bound to haemoglobin, but also to a lesser extent to plasma proteins.

CO_2 transport is also dependent on the O_2 tension or more precisely, the state of oxygenation of Hb since this affects the CO_2 binding power of the blood, i.e. reduced Hb forms more carbamino - Hb than Hb O_2 . Thus, at a given PCO_2 , fully oxygenated blood holds less CO_2 than deoxygenated blood. This effect, which thus serves to increase the efficiency of external respiration in man, is known as the Haldane effect.

Modelling the relationship between CO_2 concentration and tension in blood has been approached from two different viewpoints. Kelman (171) has

developed a description based on explicit mathematical consideration of the underlying physico-chemical equations.

A more common approach, however, (90) is to fit empirical curves to published data of experimentally derived concentration/tension relationships on certain subjects.

Surprisingly, despite the biochemical complexity of CO_2 transport in blood eluded to above, the relationship can be approximated linear over the range of physiological interest (PCO_2 : 30 - 60 mm Hg) i.e. see Fig. 2.2.

$$C_{CO_2} = a + b\,PCO_2 \qquad 2.15$$

L(STPD)/L mm Hg.

This relationship has been used in many simulations of carbon dioxide transport (143, 282, 61, 303, 175, 185). Quantitatively, little difference has been found in the slope 'b' of the "CO_2 dissociation curve" at different O_2 levels (in the same subject). However, due to the Haldane effect, the intercepts "a" are different for arterial and mixed venous blood, i.e. $a_{\bar{v}} \neq a_a$. Many workers employing the representation given by equation 2.15 do not take the Haldane effect into account in their simulations (i.e. they assume $a_{\bar{v}} = a_a$), e.g. (282). Many more do not take into account the known intersubject variation in the slope 'b' of the dissociation curve, but assume a constant value for all subjects, (143, 282, 61, 303). The cause of this subject to subject variation in 'b' is related to the corresponding variation in Hb concentration, e.g. it is well known that the slope of the dissociation curves in polycythaemics is markedly greater than in anaemics.

This relationship can be modelled and the value of 'b' thus tailored to the individual subject. Pack (228) based on an investigation by Peters et al (237) recommended that the relationship between 'b' and Hb concentration be described as :

THE CO2 DISSOCIATION CURVE

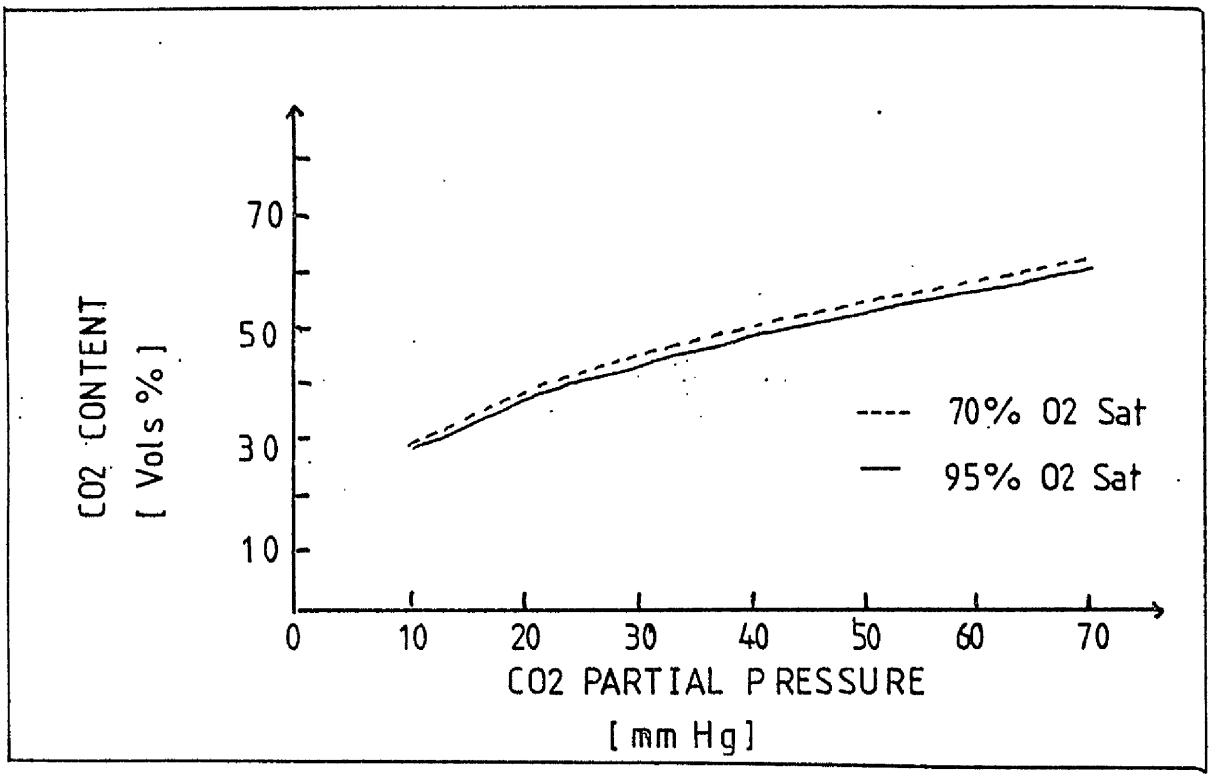


FIGURE 2·2

$$b_{L/L/mm\ Hg} = 0.448 \frac{Hb.\ conc.}{30 \times 100} + 6.3 \qquad 2.16$$

where the Hb concentration is in units of grams per 100 ml whole blood (gm%).

Thus, given the linearised CO_2 content/partial pressure relationship, the Fick equation (equation 2.4) can be written in terms of CO_2 tensions as :

$$\dot{V}_{CO_2} = \dot{Q} (C_{\bar{v}CO_2} - C_{aCO_2})$$

$$= \dot{Q}\, b (P_{\bar{v}CO_2} - P_{aCO_2}) + \dot{Q} (a_{\bar{v}} - a_a)$$

$$= \dot{Q} \left[b (P_{\bar{v}CO_2} - P_{aCO_2}) + A_{INT} \right] \qquad 2.17$$

where A_{INT} is the difference between the mixed venous and arterial CO_2 dissociation curve intercepts (taken as 0.0129 subsequently in this thesis).

2.5 Homogeneous Lung Gas Exchange Model with Flow-Through Representation of Ventilation

Equations describing the transient aspects of alveolar capillary gas exchange (i.e. dynamic equations) can be derived by recognising that, in the non-steady state, by conservation of mass the difference between the net transfer of a gas species from the environment to the lungs (as given by equation 2.3) and the net transfer between the lung gas and the blood (as given by equation 2.4) will represent the rate of change of the quantity of gas in the lungs, i.e.

Rates of change of amount of gas in the lung	=	Net transfer between ext. environment and lungs	+	Net transfer between pulmonary capillary blood and lungs.	2.18

Such a model was used in the classical respiratory control simulation of Grodins et al (143) and has since been used extensively in this area.

To overcome difficulties with the time-varying nature of ventilation and motivated by the desire to obtain an analytical solution the Grodins model utilised a conceptual "flow through" representation of ventilation, which effectively ignored the events of the respiratory cycle. This is depicted in Fig. 2.3.

Although Grodins original model (143) ignored the wasted ventilation in the upper airways (assumed zero deadspace, i.e. $\dot{V}_{A_I} = \dot{V}_I$, $\dot{V}_{A_E} = \dot{V}_E$) this was accounted for in later work by using the Bohr equation, which proportions the ventilation into the alveolar and dead space components.

i.e. $$\dot{V}_I = \dot{V}_{A_I} + \dot{V}_D = \dot{V}_{A_I} + f\ V_D \qquad 2.19$$

similarly, $$\dot{V}_E = \dot{V}_A + \dot{V}_D = \dot{V}_{A_E} + f\ V_D \qquad 2.20$$

where $\dot{V}_{A_I}$ is inspired alveolar ventilation, V_D dead space ventilation, $\dot{V}_{A_E}$ expired alveolar ventilation, $\dot{V}_I$, $\dot{V}_E$ inspired and expired minute ventilation at the mouth, V_D = dead space value and f is breathing frequency. Other assumptions inherent in the Grodins model were :

(1) the respiratory gas exchange ratio R is constant and unity (this means $\dot{V}_{A_I} = \dot{V}_{A_E} = \dot{V}$),

(2) the alveoli are assumed uniform (homogeneous) and of constant volume ($\frac{d\,V_A}{dt} = 0$),

(3) gas tensions in the alveoli and arterial blood are in continuous equilibrium (i.e. $P_A = P_a$).

GRODINS FLOW-THROUGH MODEL

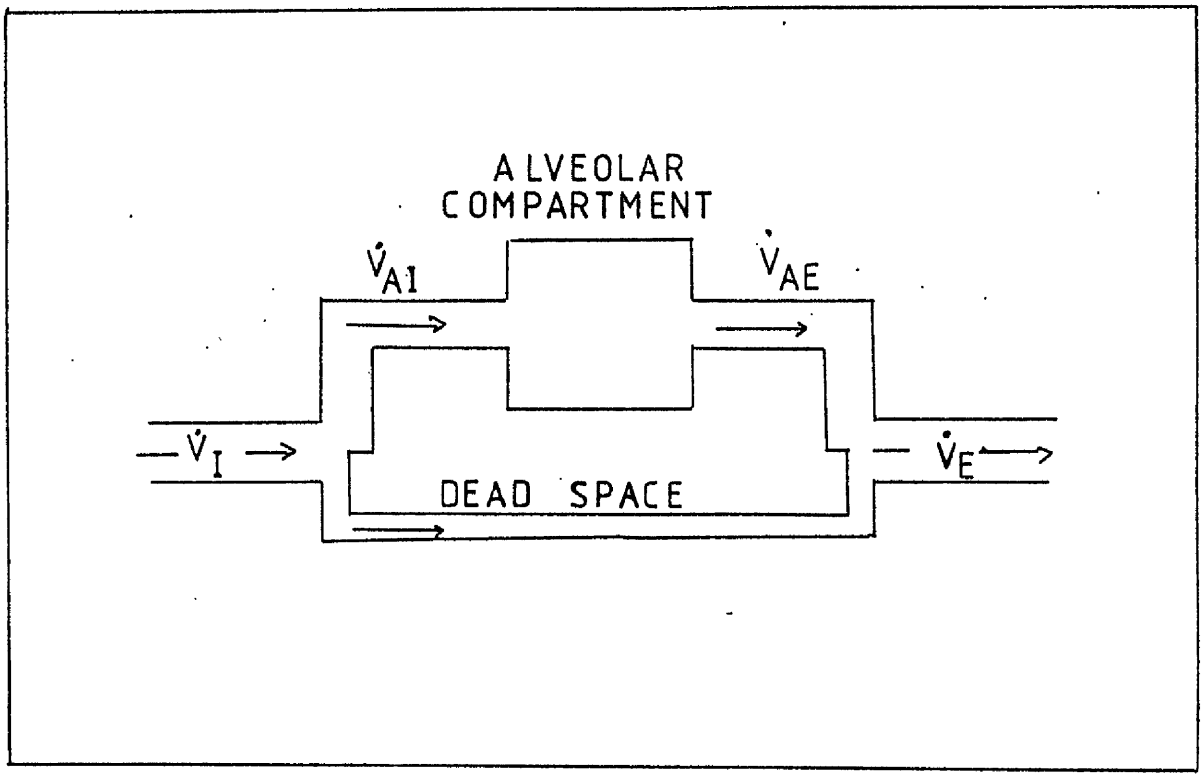


FIGURE 2·3

Thus, applying the concepts and quantities of Section 2.2 to equation 2.20 above, results in the following alveolar-capillary gas exchange equation for a gas species x .

$$\frac{d}{dt}\left(V_A F_{A_x}\right) = \dot{V}_{A_I} F_{I_x} - \dot{V}_{A_E} F_{A_x} + \dot{Q}\left(C_{\bar{v}_x} - kC_{a_x}\right) \cdot \frac{1}{k} \qquad 2.21$$

where $\frac{1}{k}$ embodies the correction from STPD to BTPS (we are working at STPD here) and is obtained from equation 2.6. Using Dalton's Law and assumption (1), equation 2.21 reduces to

$$\frac{V_A}{(B-47)} \cdot \frac{dP_{A_x}}{dt} = \frac{\dot{V}_{A_I} P_{I_x}}{(B-47)} - \frac{\dot{V}_{A_E} P_{A_x}}{(B-47)} + \dot{Q}\left(C_{\bar{v}_x} - C_{a_x}\right) \cdot \frac{B}{(B-47)} \cdot \frac{310}{273} \qquad 2.22$$

Tidying up and employing the remaining assumptions results in

$$V_A \frac{dP_{A_x}}{dt} = \dot{V}_A\left(P_{I_x} - P_{A_x}\right) + \dot{Q}\left(C_{\bar{v}_x} - f\left(P_{A_x}\right)\right) \cdot \text{const.} \qquad 2.23$$

where const $= \frac{760 \times 310}{273} = 863$ 2.24

and $f(P_{A_x})$ is the content partial pressure relationship for the gas species x . Particular choices for given gases were discussed in earlier sections.

Equation 2.23 is the basic dynamic equation of alveolar capillary gas exchange and as pointed out earlier, because V_A is assumed constant, may be solved analytically. This may be done for various gases and/or physiological conditions. $C_{\bar{v}}$ may be regarded as constant (i.e. for short experiments less than around 45 secs.) or may be obtained as a solution of one or more tissue equations in longer experiments where recirculation has occurred. Aspects of tissue store equations will be more extensively discussed in a later section of this chapter.

If an insoluble gas is used, there will be no net transfer of this gas species to the blood and the second term of the right hand side of equation 2.23 can be ignored. Alternatively, during breath-holding $\dot{V}_A$ is zero and the first term on the right hand side of equation 2.23 can be ignored.

2.6 Homogeneous Lung Gas Exchange Model with Time-Varying Representation of Ventilation

The "flow through" type of model discussed in the previous section represented a great advance over the traditional steady state models much beloved by respiratory physiologists. However; in terms of a truly "physical" description of respiratory gas transport, it is still conspicuous by its failure to consider that which, even to the layman, would appear the most distinguishing facet of the system, that is the time-varying nature of ventilation.

There are, of course, fairly sound reasons for this omission. The complex process of gas transport in the airways can only really be properly described by distributed models (58, 231). The mathematics and resultant computation involved in this is rather overbearing.

However, a more adequate structural representation of gas transport in the upper airways than is furnished by the Grodins model is a necessary pre-requisite for the use of this type of model in such applications as indirect measurement in the individual subject. Fortunately, if one is willing to accept a degree of flexibility, fairly tractible lumped parameter descriptions of upper airways transport behaviour can be formed without recourse to a full distributed solution. Motivated by such aspirations, Dr. Murray-Smith, Dr. Pack and associates at the C.R.I. and in this University Department, viewed the pulmonary component of this model in the form illustrated in Figure 2.4, i.e.

PULMONARY COMPONENT OF CYCLIC MODEL

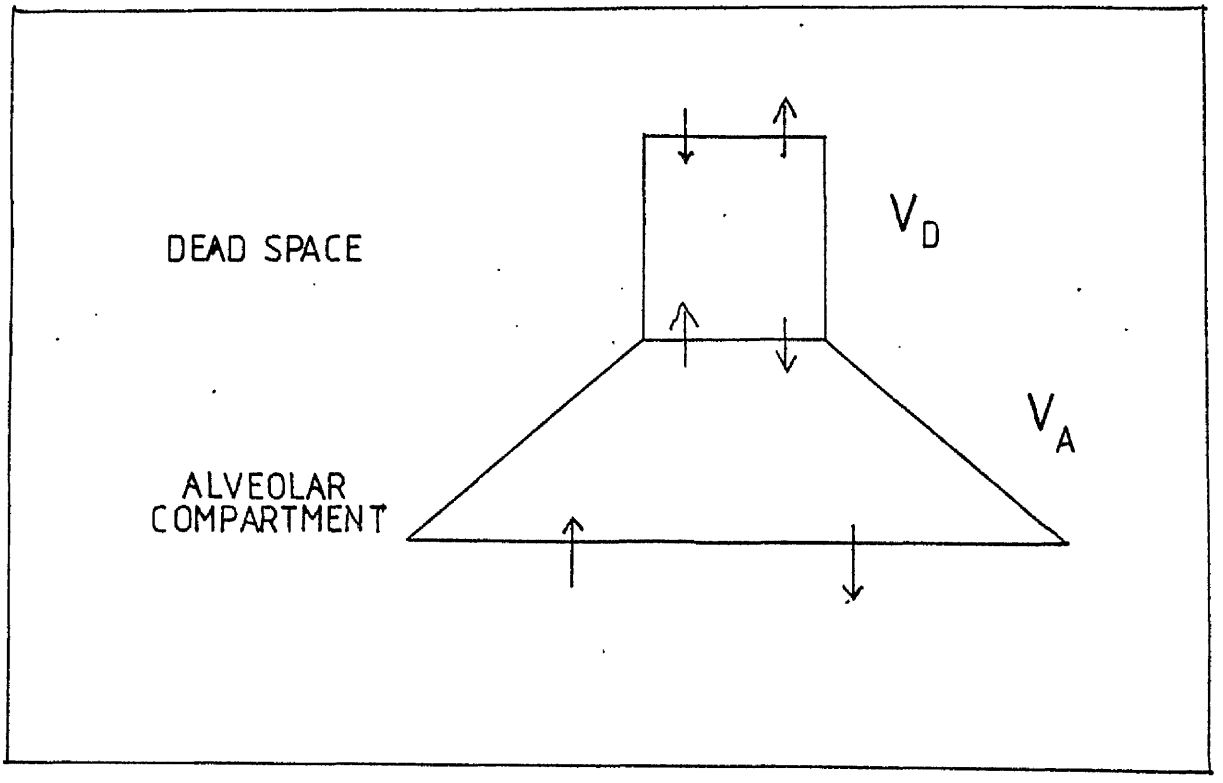


FIGURE 2·4

(i) conducting airways - A rigid "non-reacting" dead space compartment in which no volume change can occur,

(ii) Alveoli - where volume change can occur.

(This of course is no more than the Bohr conceptualisation of lung structure). They also postulated that gas washes in and out of the airways with a plane front (i.e."plug flow" in the airways).

Such assumptions above would dictate that the inspired/expired gas concentration profile would be of the square wave form. Although this may seem on the surface a gross simplification of the true state of nature, it is a matter of empirical fact that such a waveform can readily be discerned in expired gas concentration records logged at the mouths of real subjects, e.g. see Figure 2.6(b). It is this factor which has encouraged subsequent development of the model. In fact, many authors have attempted to incorporate the cyclic nature of ventilation into equations of the type 2.23 (e.g. 271, 302, 222), but only in theoretical studies - no attempt has been made to apply them to measurement of physiological quantities.

Utilising the concepts detailed above, Pack and his associates (96, 214, 229) considered gas exchange in the respiratory cycle in terms of three separate stages outlined below.

STAGE	CONDITION
(S1) Inspiration of dead space gas to alveoli	$\dot{V} \geqslant 0$ and $\int_{t_I}^{t} \dot{V}_I \, dt < V_D$
(S2) Inspiration of atmospheric gas to alveoli	$\dot{V} \geqslant 0$ and $\int_{t_I}^{t} \dot{V}_I \, dt \geqslant V_D$
(S3) Expiration	$\dot{V} < 0$

where $t = t_I$ defines the start of inspiration.

The transfer of gas into and out of the lungs is different in all three of these stages of the respiratory cycle. Applying the concept of conservation of mass

over all three of these stages we arrive at the following equation analogous to equation 2.18.

Rate of change of amount of gas in the lung	=	Transfer from dead space (during stage 1)	+	Transfer for ext. environment (during stage 2)

2.25

+	Transfer to dead space (during stage 3)	+	Transfer from blood (during all stages)

Mathematically this can be written

$$\frac{d}{dt}(V_A F_{A_x}) = S_1 \dot{V} F_{D_x} + S_2 \dot{V} F_{I_x} + S_3 \dot{V} F_{A_x} + \dot{Q}(C_{\bar{v}_x} - C_{a_x}) \cdot \frac{1}{k} \qquad 2.26$$

$$= \frac{d}{dt}(V_A P_{A_x}) = S_1 \dot{V} P_{D_x} + S_2 \dot{V} P_{I_x} + S_3 \dot{V} P_{A_x} + \dot{Q}(C_{\bar{v}_x} - f(P_{A_x})) \quad \text{const.} \qquad 2.27$$

where $S_1 = 1$ only during the condition described for stage 1 above and 0 otherwise; similarly for S_2 and S_3.

In the previous section V_A was considered as fixed, however, in reality V_A will vary with time as follows :

$$V_A = V_A(t) = V_{A(0)} + \int \dot{V}\, dt - \int \dot{V}_{O_2}\, dt + \int \dot{V}_{C_{O_2}}\, dt \qquad 2.28$$

(FRC)

Now, if the variation in V_A due to the difference in gas flux to and from the blood can be neglected, i.e. if respiratory exchange ratio is assumed equal to one, the last two terms of this equation cancel out and we have

$$V_A = V_{A(0)} + \int \dot{V}\, dt \Rightarrow \frac{d V_A}{dt} = \dot{V} \qquad 2.29$$

and equation 2.27 becomes

$$V_A \frac{d P_{A_x}}{dt} = S_1 \dot{V}(P_{D_x} - P_{A_x}) + S_2 \dot{V}(P_{I_x} - P_{A_x}) + \dot{Q}(C_{\bar{v}_x} - f(P_{A_x})) \text{ const.} \quad 2.30$$

Note that V_A in this equation in addition to being time-varying as defined by equation 2.29, is an 'equivalent' lung volume since in addition to the volume component of the gas species in lung gas, it will also contain a component from the gas dissolved in lung tissue (and assumed to be in equilibrium with lung gas) expressed as an equivalent additional volume; see Pack(228)for further discussion. Now what of P_{D_x} ? Obviously; since there is "plug flow" through the dead space, P_{D_x} should be a suitably time-delayed version of P_{A_x}.

$$P_{D_x} = P_{A_x}(t - \tau) \quad 2.31$$

This time delay will be flow dependent and defined by the following equation

$$\int_{tI}^{t} |\dot{V}_I| \, dt = \int_{t_I - \lambda}^{t} |\dot{V}_E| \, dt \quad 2.32$$

However, this will be complex to simulate.

In earlier work Pack et al (229) assumed that P_{D_x} be set equal to P_{A_x} over stage 1, i.e. they assumed the first term on the right hand side of equation 2.30 is zero.

Note that with this formulation there is no need to actually measure expired flow since it does not appear in the alveolar-capillary gas exchange equation. This was advantageous since there are difficulties in measuring this quantity with a conventional pneumotachometer mainly associated with the fact that expired gas is saturated with water vapour. However, more recently at C.R.I. this advantage has been negated due to the availability of

a pneumotach specially designed to handle 'wet' gas (284). Thus, Gray (139) has proposed the following formula for P_{D_x} (assumed constant over stage 1) which utilises expired ventilation.

$$P_{D_x} = \frac{\int_{t_x}^{t_I} \dot{V}_E P_{A_x} \, dt}{\int_{t_x}^{t_I} \dot{V}_E \, dt} \qquad 2.33$$

where t_x is such that $\int_{t_x}^{t_I} | \dot{V}_E | \, dt = V_D$ 2.34

i.e. P_{D_x} in the first dead space of inspiration is taken as the flow-weighted mean of P_{A_x} over the last dead space of the previous inspiration.

In fact, it transpires this is similar to the expression developed by Hlastala (154) except that the linear mixing term included by this author over the inspired volume range from 50 ml less to 50 ml greater than the dead space has been omitted.

Thus, to summarise,equation 2.30 can be most conveniently written as follows :

$$V_A \frac{d P_{A_x}}{dt} = S \dot{V} (P_{I_x}^* - P_{A_x}) + \dot{Q} (C_{\bar{v}_x} - f (P_{A_x}) \text{ const} \qquad 2.35a$$

where $S = 1$, $\dot{V} > 0$, $= 0$ otherwise,

$$\begin{aligned} P_{I_x}^* &= P_{D_x} \text{ (as given by eqn. 2.33) if } S_1 = 1 \\ &= P_{I_x} \qquad\qquad\qquad\qquad \text{if } S_2 = 1 \end{aligned} \qquad 2.35b$$

In this form the similarity with equation 2.27 can be more readily appreciated. For carbon dioxide the above equation thus reduces to the following form

$$V_A \frac{dP_A}{dt} = \dot{S}\dot{V}(P_I^* - P_A) + \dot{Q}\left[b\,(P_{\bar{v}} - P_A) + A_{INT}\right] \quad \text{const} \qquad 2.36$$

2.7 Modelling the Arterial - Mixed Venous Loop

As mentioned in section 2.4, transient changes in alveolar-capillary gas levels will ultimately be reflected in mixed venous blood gas levels after recirculation has occurred. Thus in this situation modelling of this arterial-mixed venous loop is necessary. The rate of change of mixed venous gas concentrations will be determined by the dynamics of the various tissue stores in the body (i.e. muscle, fat, etc.) for the gas under consideration and on the delays, arterial and venous inherent in the blood circulatory system. Of these delays the arterial delay (τ_a) is approximately one order of magnitude less than the venous delay ($\tau_{\bar{v}}$) and is, therefore, usually neglected. Also, for the respiratory gases O_2 and CO_2 arterial/venous gas transfer will also be affected by the relevant metabolic uptake/production of these gases in the tissues themselves.

The various tissue stores, therefore, can be considered as a lumped parallel (or equivalently series) system of compartments each with a differing time constant, depending on its relative perfusion, volume, metabolic uptake/demand where appropriate and particular content-partial pressure relationship for that particular tissue type and gas species under consideration. Such a multi-compartmental modelling approach to tissue stores first appears to have been proposed by Fahri and Rahn (101, 102). Mapleson (200) evolved a similar parallel model, but his motivation was to consider the uptake of anaesthetic agents. Mapleson's model and associated parameter values has since been used and refined by himself and other authors (309, 310, 210). For any gas species x (ignoring arterial circulatory delays, i.e. $\tau_a = 0$) dynamic equations for the ith parallel tissue compartment can be written based on

conservation of mass as follows :

rate of change of amount of gas in tissue store = metabolic input term (where appropriate) - net transfer to lungs

2.37

i.e. mathematically

$$\dot{V}_{TC_{i_x}} = d\,\frac{C_{TC_{i_x}}}{dt} = \dot{M}_{i_x} - \dot{Q}_{i_x}\left[\,C_{TC_{i_x}} - C_{a_x}\,\right] \qquad 2.38$$

where the subscript TC refers to a tissue compartment. If the compartments are assumed to be arranged in parallel, as is customary, the mixed venous concentration ($C_{\bar{v}}$) will be equal to the perfusion weighted mean ($C_{\bar{TC}}$) of the concentrations in the individual tissue compartments suitably delayed by the venous circulatory time delay $\tau_{\bar{v}}$, i.e.

$$C_{\bar{v}}(t) = C_{\bar{TC}}(t - \tau_{\bar{v}}) \qquad 2.39.$$

where

$$C_{\bar{TC}} = \frac{\sum_{i=1}^{\text{No. of compts.}} \dot{Q}_i\, C_{TC_i}}{\sum_{i=1}^{\text{No. of compts.}} \dot{Q}_i} \qquad 2.40$$

For experiments of relatively short duration (i.e. of the order of minutes) for certain gas species such multi-compartment tissue representations may be over-complex. In particular, there is evidence of this for CO_2 where e.g. Cherniack et al (60) and Longobardo et al (193) both found that experimental changes in mixed venous blood occurred more rapidly than the multi-compartmental model based on a priori physiological knowledge could predict. Two hypotheses have been advanced to explain this 'fast' CO_2 tissue storage.

(1) The apparently small CO_2 tissue storage volume is due to the barrier between intercellular and extra-cellular fluid being diffusion limited (Fowle and Campbell (117)).

(2) Certain enzymes (primarily carbonic anhydrase) are necessary for CO_2 hydration (see section 2.4). These may not exist in certain tissues, e.g. muscle. Thus, these tissues would respond initially to raised CO_2 levels with an absorptive capacity of CO_2 identical to water (i.e. equivalent to a low slope of CO_2 dissociation curve). (Longobardo et al (193)).

The weight of evidence tends to support the latter hypothesis (36,37).
To circumvent the above difficulty in the model of the type given by equation 2.38, Longobardo et al (193) utilised the concept of an "effective tissue volume" $V_{TC\ eff}$ for CO_2 smaller than the apparent "physical" tissue volume and defined as

$$V_{TC\ eff} = V_{TC} \cdot \frac{b\ (\text{tissues})}{b\ (\text{blood})} \qquad 2.41$$

to better explain their experimental observations. Such an idea was also taken up by Pack et al (229) in their single tissue compartment CO_2 model intended for short duration experiments. This model also ignores for simplicity the venous circulatory veneous delay (i.e. $P_{\bar{v}} = P_{TC}$) and also analogous to their alveolar-capillary CO_2 equation (equation 2.36), alveolar-arterial equilibrium is assumed ($P_A = P_a$). Thus, the equation is

$$b\, V_{TC}\, d\, \frac{P_{TC}}{dt} = \dot{M} - \dot{Q}\left[b\ (P_{TC} - P_A) + A_{INT}\right] \qquad 2.42$$

Note the V_{TC} is an effective tissue volume which means "b" on the right hand side of this equation is the dissociation slope for CO_2 in the blood.

2.8 Potential of the Homogeneous CO_2 Model for use in Indirect Measurement of Cardio-Pulmonary Parameters

Based on ideas presented in previous sections of this chapter, a parsimonious model of gas transport in the lungs and tissues is illustrated schematically for the particular case of CO_2 in Figure 2.5. The associated equations are given below :

$$V_A \frac{dP_A}{dt} = S\dot{V}(P_I^* - P_A) + \dot{Q}\left[b\ (P_{TC} - P_A) + A_{INT}\right]\ \text{const.} \qquad 2.43$$

$$b\,V_{TC} \frac{dP_{TC}}{dt} = \dot{M} - \dot{Q}\left[b\ (P_{TC} - P_A) + A_{INT}\right] \qquad 2.44$$

These equations are assumed to embody the physiological knowledge and assumptions discussed earlier in this chapter.

Analogous equations to the above can be written for O_2 and inert gases by employing the appropriate concentration/partial pressure relationship for these gases.

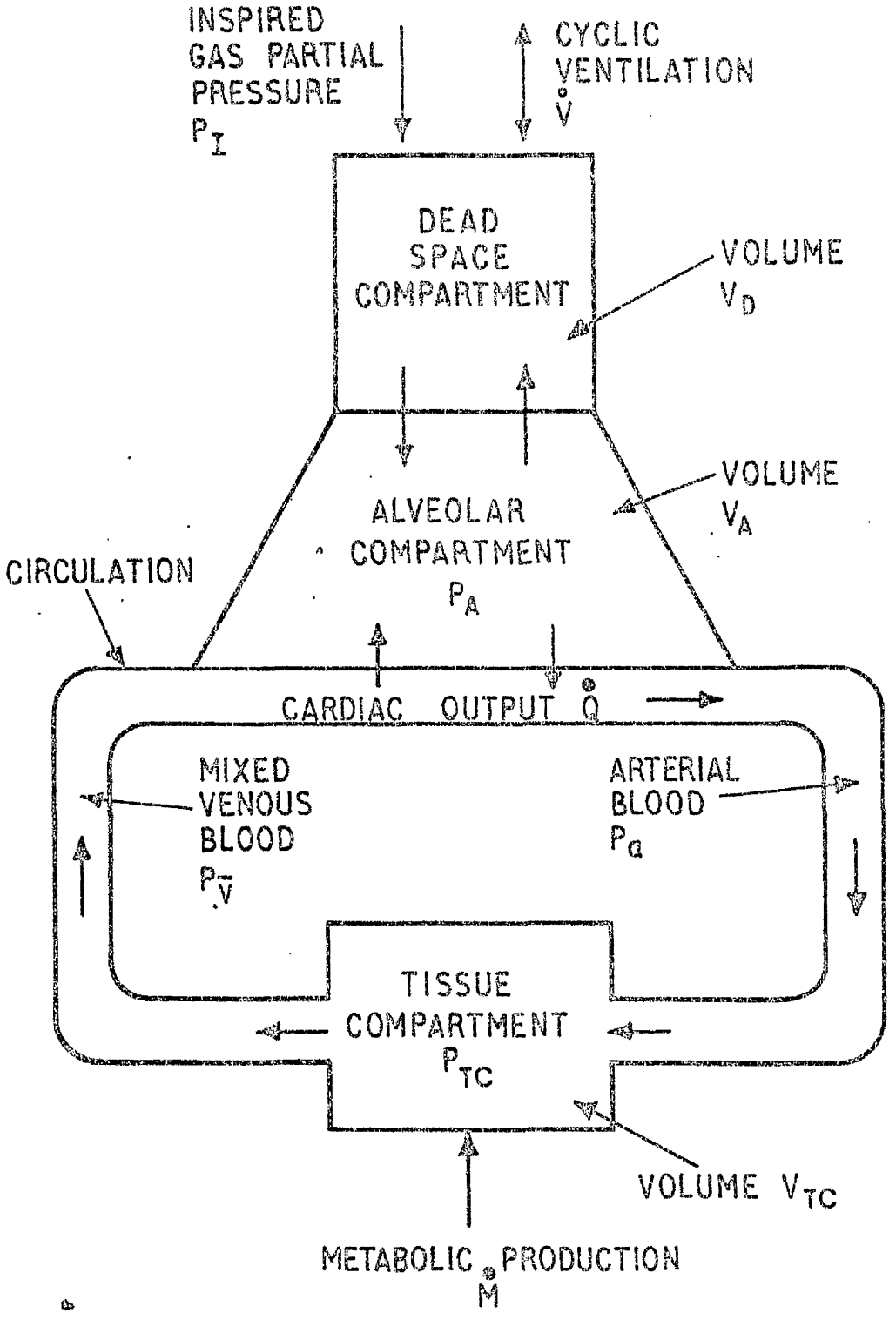
The behaviour of the CO_2 model to controlled changes in input (P_I) may be conveniently investigated using digital simulation. The response of the model to a unit step in P_I at 40 secs. is shown in Figure 2.6(a). In this simulation, for lack of anything better, a sinusoidal representation of ventilation is assumed.

$$\text{i.e. } \dot{V} = \dot{V}_{max} \sin 2\pi f t \qquad 2.45$$

where f is breathing frequency and $\dot{V}_{max}$ the amplitude of the sinusoidal is calculated from average minute ventilation $\dot{V}_{av}$ as

$$\dot{V}_{max} = \pi \dot{V}_{av} \qquad 2.46$$

From the response characteristics in Fig. 2.6(a) we can see the model behaves as a damped second order system, (i.e. in control terminology a system with two real left hand plane poles). It is pertinent to ask if this



HOMOGENEOUS GAS TRANSPORT MODEL
(CARBON DIOXIDE)

FIGURE 2.5

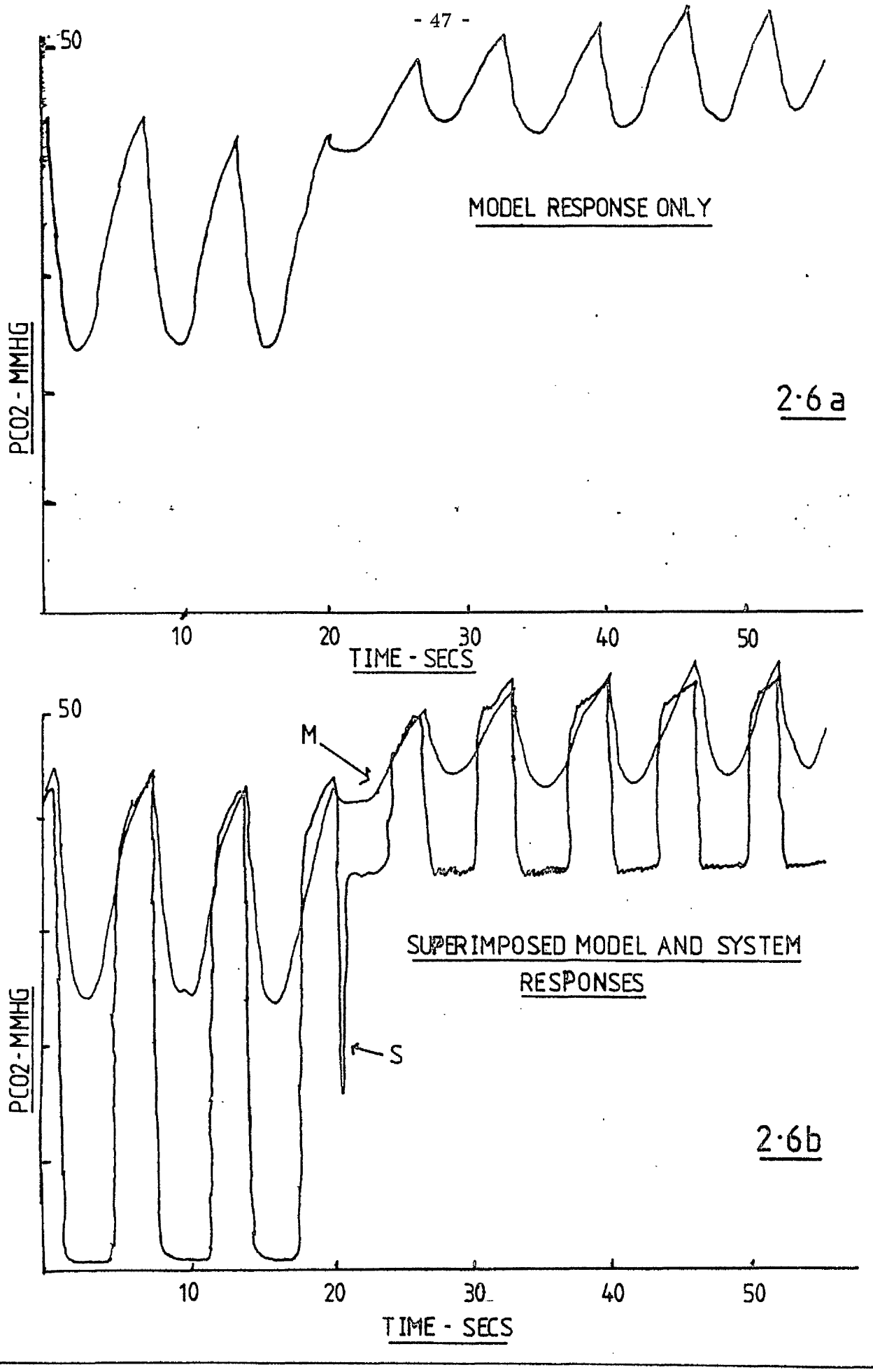


FIGURE 2-6 MODEL AND SYSTEM OUTPUTS.

behaviour is mimicked by the 'real' system. Thus, for comparison, in Figure 2.6(b) the PCO_2 of a real subject in response to a similar stimulus is shown as measured at the mouth, with the model response overlayed.

Although on first examinaton model and real subject responses appear very different, it has to be borne in mind that the model is essentially reflecting events in the lungs whilst the PCO_2 of the subject is measured at the mouth. However, if we compare model and subject over the end-expiratory region, where gas concentrations as measured at the mouth should reflect alveolar gas levels (at least for homogeneous lungs), it can be seen that the two responses are not entirely dissimilar.

Although sinusoidal ventilation has been used in the simulation above, in principle, there is no reason a subject's measured ventilation can't be used to drive the model, which thus can then be subjected to an identical change in controlled input, to that of the real system.

Intuitively then, under these conditions (if the model is a 'good' representation of the real system structure) the only mechanism by which the model output can be dissimilar to that of the system over the end-tidal region is if the internal parameters (constants) are different from the corresponding physiological quantities in the real system.

Therefore, as realised by Dr. Murray-Smith, Dr. Pack and co-workers at C.R.I. and this Department, this suggests a means of indirectly inferring the physiological quantities of the real system by manipulating the model parameters until input/output correspondence of the model and real system is achieved. Such a technique is, of course, nothing more than Parameter Estimation much used in an industrial control systems context and discussed with reference to biological (biomedical systems) in Chapter 1.

It is obvious that this exercise will only be meaningful if measurement of these cardio-pulmonary parameters is particularly valuable. In fact, there is considerable clinical interest in indirect measurement of one of these particular parameters. That is, the parameter $\dot{Q}$ the pulmonary blood flow rate or cardiac output in normal subjects. Traditional techniques for measuring this are invasive and at the very least, involve some discomfort to the patient and thus, accurate measurement methods would be advantageous.

It was this movitation to measure cardiac output which led to the joint development of the parameter estimation technique by this Department and C.R.I.

Attempting to elevate this technique from abstract concept to a useful clinical tool has involved considerable effort with many problems to be overcome (e.g. synchronisation for comparison purposes of model output (at alveolar level) with system output (as measured at the mouth)). This project has thus consumed the attentions of a number of workers and the author is only the latest of these.

In the next chapter, therefore, it is relevant to summarise the status of this project around the time the author became involved and the experimental set-up developed for the work, together with some preliminary results.

CHAPTER 3

NON-INVASIVE MEASUREMENT OF CARDIAC OUTPUT USING A HOMOGENEOUS CO_2 GAS TRANSPORT MODEL

3.1 Introduction

Most physicians would agree that the output of the heart (the cardiac output in L/M) could form a most important index of cardio-vascular function. Such a measurement could be useful in patient monitoring (e.g. during cardio-thoracic surgery or in intensive care) and also in numerous physiological investigations. However, the most direct method of obtaining this quantity, i.e. by surgical implantation of a flow meter in the pulmonary artery, is obviously unethical in man. It has also been shown that, contrary to what one might think, there is little correlation between cardiac output and more easily measured quantities such as pulse rate and blood pressure. Therefore, recourse must be made to less direct techniques.

Many indirect methods of measuring cardiac output have been developed over the years. As we shall see in the following section, however, most of these have serious disadvantages and, therefore, despite their promise have made little impact. Thus, a technique which overcomes these deficiencies would have widespread applicability. It is hoped that the method based on the CO_2 gas transport model, to be outlined in this chapter, will constitute such a method. To be technically correct, our technique measures pulmonary blood flow rather than cardiac output. Current physiological opinion, however, suggests the difference between the two is trivial except in subjects where the right to left shunt is several times higher than normal.

As noted in the previous chapter, the new technique was already under active development prior to the involvement of the author in the project. The feasibility of making measurements of physiologically important variables by the use of non-steady state techniques had become apparent at an early stage (96, 230). This, however, was followed by a long period of very slow

progression towards a solution of the problems of producing a practical tool, (228, 234). This was still very much underway when the author became associated with the work. Only around early 1977 had the model and the data processing techniques reached such a stage of refinement as to allow the method to be exploited in larger numbers of observations and to contemplate comparison with another established technique.

This chapter details these validation studies in which the author became involved in the initial stages of his work on the project. It is pertinent to point out that these experiments were carried out before the informational aspect of the problem (with which much of the rest of this thesis is concerned) had begun to be explored.

The computational and experimental bases of the model-based, non-invasive measurement method will be discussed in Sections 3.3 and 3.4. In the next section, however, a review of other methods of cardiac measurement presently known is in order to place the new one in perspective.

3.2 Methods of Cardiac Output Measurement

Almost all schemes for cardiac output measurement, which have been developed over the years, are based in one way or another on an application of the Fick dilution principle (equation 2.4) which was introduced in the previous chapter.

$$\dot{Q} = \frac{\dot{V}_x}{(C_{a_x} - C_{\bar{v}_x})} \qquad 3.1$$

In this chapter $\dot{V}_x$ can be taken to mean the rate of uptake or removal of any tracer x introduced at the lungs, and C_{a_x} and $C_{\bar{v}_x}$ the corresponding resultant arterial and mixed venous tracer concentrations. This basic relationship holds whether the reference substance be a gas, a dye of some

kind, a radioactive isotope or a physical agent like heat.

Historically the most used clinical method for measuring cardiac output has been the "Direct Fick" method (148). In this method mixed venous and arterial blood content (as required to solve equation 3.1) are measured directly from blood samples obtained by cardiac catheter. Oxygen is the preferred reference gas.

Next in prominence are the so called indicator dilution methods. In the dye dilution technique (194), a known quantity of dye is injected into a central vein. This will eventually appear in the arterial blood. At this point the time course of its concentration is continuously sampled to obtain a clearance curve. Cardiac output is obtained by relating the amount of dye injected to the area under the primary portion of the curve. This, in effect, utilises the integral form of the Fick equation, i.e.

$$\dot{Q} = \frac{m}{\int C(t)\, dt} \qquad 3.2$$

m being the mass of dye injected and C(t) its down stream concentration.

The principle behind the thermal dilution technique (194) is similar except the indicator substance is a cold solution, the temperature clearance curve for which is inferred by a thermistor placed at the end of a catheter inserted in the pulmonary artery.

A serious drawback of the techniques discussed so far is, obviously, that they require heart catheterisation and/or arterial puncture. That is they are invasive. However, their main advantage is that they are generally more accurate than the more bloodless methods so far devised. They, therefore, remain the yardstick against which all new techniques must ultimately be judged.

Many non-invasive methods for measuring cardiac output have been

proposed in the past. In fact, all the quantities in equation 3.2 can be easily measured directly except $C_{\bar{v}_x}$, the mixed venous concentration. It is in estimating this quantity that the difference in the approaches lie. For CO_2, $C_{\bar{v}}$ can be estimated by employing the lungs as a tonometer, i.e. by allowing alveolar gas to equilibrate with mixed venous blood during a ventilatory manoeuvre. In the so-called rebreathing methods PCO_2 is measured either at points of actual equilibrium (Collier's "plateau" method (65,7,165)) or extrapolated by the analysis of the rate of change of PCO_2 (Defares' "exponential extrapolation" method (80, 164, 109)) during the rebreathing manoeuvre. $C_{\bar{v}CO_2}$ can also be inferred on the basis of analysis of alveolar gas at different breath-holding times (107, 177) or on the basis of a single prolonged expiration (175). For a useful review of these methods and further modifications see (100).

Comparison of the Defares and Colliers methods has been carried out recently by Godfrey and Wolfe (127). These authors conclude that the "plateau" method gives more reproducible results. The work of Franciosa et al (122) also suggests this. As regards accuracy, both rebreathing methods have been generally found to be less reproducible than the more direct cardiac output estimation methods, especially at rest (243). In fact, to quote the very recent paper of Reybrouck et al (173), "At rest the validity of the CO_2 rebreathing method to determine $\dot{Q}$ remains questionable".

Similar methods to the above, but based on O_2 analysis, were initially proposed by Burwell and Robinson (54). More recently, these have been taken up by Cerretelli et al (57). Serious problems with this class of methods (associated with deriving $C_{\bar{v}O_2}$ under conditions where there may be a shift in the O_2 dissociation curve, e.g. during exercise) have been reported (99, 73). Criticisms seem to have killed off further developments in this direction.

Another class of methods involves the use of soluble, but biologically inert gas (à la Kety (173)) as the reference substance in equation 3.1. The rationale behind the use of such a gas is that during initial uptake (i.e. before recirculation occurs), -the mixed venous concentration will be zero, thus apparently considerably simplifying solution of the Fick equation. In practice, however, another difficulty arises in that it is now necessary to know the storage capacity of the tracer gas in the lung tissue. One is faced with the dilemma of assuming a standard value of this quantity for the gas in question (e.g. see (173)), or further complicating the experimental procedure, i.e. using two additional tracer gases (252) to determine it.

The most extensively used gases in 'inert gas' methods have been acetylene (144, 8) and nitrous oxide (23, 19, 308). More formal parameter estimation and system identification procedures have also been applied in various ways to try to measure cardiac output.

In a non-invasive measurement scheme, Maloney and Bekey (197) applied a discrete gradient parameter identification algorithm (24) to a CO_2 gas exchange model, similar to the type discussed in Section 2.5 of Chapter 2. Only the cardiac output parameter was adjusted in this technique. The other parameters inherent in the model were either inferred from published figures in the literature, or estimated by other means. Despite this, excellent results in terms of agreement with simultaneous dye-dilution measurements have been reported with this technique during air breathing experiments with dogs (197). However, a later publication (27) has cast severe doubts on the credibility of this technique in that it has shown that the cardiac output estimates obtained are heavily dependent on the choice of initial CO_2 tissue partial pressure,

a model parameter which is fixed in advance from the literature. In fact, sensitivity studies showed that a 10% change in the assumed initial CO_2 tissue partial pressure produces approximately a 100% change in the cardiac output estimates. It is evident from this analysis that the technique is potentially inaccurate unless better a priori estimates of initial tissue CO_2 partial pressure are obtained, i.e. via venous blood samples. However, under these conditions the technique will no longer be non-invasive.

Etsyon et al (96A) describe an estimation procedure utilising a model which is essentially a modification of that of Saidel et al (253). This is an interesting study in that it addresses the question of the sensitivity of the estimates to experimental errors (both systematic and random). No experimental results with the method are reported in this paper, however.

A combined $O_2/CO_2/N_2$ model has been employed by Homer and Denysyk (155) to estimate cardiac output during a 30 second rebreathing manoeuvre in dogs. The criterion function used by these authors to determine goodness of fit between model and data is the weighted sum of squares between model prediction and measurement of alveolar PCO_2, PO_2 and PN_2. The authors claim that such use of a multiple gas model greatly stabilises the numerical estimation problem. In fact (as we will show in Chapter 7 of this thesis), the O_2 and N_2 portions of the model are largely redundant since the results will be determined almost completely by the CO_2 component of the model. Homer and Denysyk eliminate the model/data synchronisation problem, introduced in Chapter 2, Section 2.8, by taking measurements endotracheally, i.e. directly at the inlet to the alveoli. Thus, model and data can be compared more directly. Note, however, that the technique in this form cannot be classed as non-invasive and as such, is not really suitable for human application.

Methods based on inert gas models have also been used. Stout et al (269) use a nitrous oxide model and report results which are in reasonable agreement ($\pm$ 20%) with simultaneous cardiac output estimates obtained using the "Direct Fick" method in experiments with five anaethetised dogs. Zwart et al (309) obtain estimates of ventilation perfusion ratio by a frequency response method applied to an inert gas model. Halothane is the test gas in this application. This is applied sinusoidally at a frequency arranged to be higher than the assumed break point frequency of body gas uptake. The authors show how this particular choice of tracer agent and forcing function frequency helps reduce the effects of errors in mixed venous blood gas concentration on the resultant estimates.

Finally, some published results for some of the cardiac output measurements techniques in terms of repeatability and comparability are detailed in Tables 3.1 and 3.2. These will be referred back to at a later stage in this thesis when we compare these figures with results obtained from the method used in the present study.

TABLE 3.1

REPRODUCIBILITY ACHIEVED BY VARIOUS $\dot{Q}$ MEASUREMENT METHODS REPORTED IN THE LITERATURE

Investigation	Method	Experimental Details	Coefficient of Variation
Franciosa et al (122)	Dye Dilution	Supine Rest CHD/Hypertensives	6.5%
Franciosa et al (122)	Collier CO_2 rebreathing	Supine Rest CHD/Hypertensives	6.0%
Ferguson et al (109)	Defares CO_2 rebreathing	Sitting rest normal men	13.3%
Ferguson et al (109)	Defares CO_2 rebreathing	Sitting exercise normal men	5.5%
Becklake et al (23)	N_2O rebreathing	Sitting and treadmill Adults	8.5%
Ayotte et al (19)	N_2O rebreathing	Rest / exercise Adults	7.1%
Homer and Denysyk (155)	O_2, CO_2, N_2 model	Rest/exercise/shock dogs.	15%

TABLE 3.2

COMPARABILITY RESULTS OF VARIOUS $\dot{Q}$ MEASUREMENT METHODS REPORTED IN THE LITERATURE

Investigation	Methods Compared	Experimental Details	Differences	r
Franciosa et al (122)	Dye dilution vs. Collier CO_2 rebreathing	Supine rest CHD/Hypertensives	25/29 ± 15%	0.93
Reybrouck et al (243)	Direct Fick vs. Defares CO_2 rebreathing	Sitting/supine Rest Hypertensives	13/25 ± 10%	0.65
Reybrouck et al (243)	Direct Fick vs. Defares CO_2 rebreathing	Exercise Hypertensives	30/34 ± 10%	0.96
Ferguson et al (109)	Dye dilution vs. Defares CO_2 rebreathing	Sitting rest normal men	8/12 ± 25%	-
Ferguson et al (109)	Dye dilution vs. Defares CO_2 rebreathing	Sitting exercise normal men	36/37 ± 25%	-
Ayotte et al (19)	Dye dilution vs. N_2O rebreathing	Rest/exercise Adults	34/36 ± 15%	0.94
Becklake et al (23)	Dye dilution vs. N_2O rebreathing	Sitting and treadmill Adults	25/26 ± 20%	-
Homer and Denysyk (155)	Dye dilution vs. O_2, CO_2, N_2 model	Rest/exercise/shock dogs.	27/36 ± 20%	-

3.3 Using the CO_2 Gas Transport Model for Parameter Estimation

To use the CO_2 gas transport model developed in Chapter 2 for parameter estimation, it is necessary to define a criterion of goodness of fit between the model and patient data and establish a mechanism whereby the parameters of the model can be automatically adjusted to achieve a minimum of this criterion. This latter aspect of the technique, i.e. that of function minimisation, is discussed in Chapter 5 and Chapter 6. The question of model/data comparison will be addressed in this section.

It was pointed out in passing in Chapter 2, Section 2.8, that the model in its given form describes events happening in the lungs. However, if the model-based estimation method is to be truly non-invasive (i.e. not like that of Homer and Denysyk (155))then for comparison purposes the only measurements we will have available will be those taken at the subjects lips.

The criterion function used in the earlier work of Pearson (234) was based on a sum of squares of the difference between model prediction and measured PCO_2 at the mouth during the end-expiratory phase of each breath. This is the only breath phase over which model and data may be meaningfully compared. The criterion function is of the form

$$J = \sum_{i=1}^{n} \left[\sum_{j=1}^{m(i)} (P^*CO_2(j) - PCO_2(j))^2 \right] \qquad 3.3$$

where P^*CO_2 is the model prediction, PCO_2 the patient PCO_2, n the number of breaths in the experiment and m(i) the number of data samples in the end tidal phase of the breath.

A problem with this criterion arises due to the fact that it is not just comparing breath by breath changes in PCO_2, but also changes in PCO_2

within a breath. This leads to the estimation algorithm attempting to fit the model to the slope in alveolar PCO_2 which arises during expiration. In view of the uncertainty as to the precise nature of the mechanism determining the expired CO_2 concentration profile, this criterion function was felt to be inappropriate bearing in mind the simplicity of the model in this area.

The next step in the work was to overcome this objection by comparing the model's performance with the <u>average</u> PCO_2 during the end-tidal part of the breath, i.e.

$$J = \sum_{i=1}^{n} \left[\sum_{j=1}^{m(i)} \frac{P^*CO_2}{m(j)} - \sum_{j=1}^{m(i)} \frac{PCO_2(j)}{m(i)} \right]^2 \qquad 3.4$$

Although this criterion is an improvement on equation 3.3, it is still deficient in the following. Firstly, it unduly weights the average for any breath-holding period occurring at the end of a breath. Secondly, it makes no allowance for the fact that there is a time delay corresponding to the time taken for the gas to traverse one deadspace, before events happening in the lungs can be observed at the mouth, i.e. patient data at time x say should properly be compared with model prediction at a time corresponding to one dead space transit time interval before time x .

These considerations have led finally to the following criterion function which is that used in the present work. In this model and data are compared on the basis of their flow-weighted means over their respective end-tidal regions as follows :

$$\overline{P^*CO_2} = \sum_{i=M_1}^{M_2} \frac{P^*CO_2(i)\ \dot{V}(i)}{\sum_{i=M_1}^{M_2} \dot{V}(i)} \qquad 3.5$$

$$\bar{P}CO_2 = \frac{\sum_{i=D_1}^{D_2} PCO_2(i)\ \dot{V}(i)}{\sum_{i=D_1}^{D_2} \dot{V}(i)} \qquad 3.6$$

$$J = \sum_{i=1}^{n} \left(\bar{P}^* CO_2 - \bar{P}CO_2 \right)^2 \qquad 3.7$$

$\bar{P}^* CO_2$ is the flow weighted mean of the model prediction and $\bar{P}CO_2$ the flow weighted mean of the patient data. The delay within the dead space is allowed for in the following manner. The model recognises the start of the end-tidal period (M_1) as one dead space from the beginning of expiration. The end point of the period (M_2) is defined as the point at which expired volume is tidal volume minus dead space, i.e. one dead space from the end of expiration. The patient data end-tidal period (D_1) is measured from the point where expired volume becomes greater than twice the deadspace (to make certain of being on the end-tidal 'plateau'). The end of the end-tidal period (D_2) is where the measured value of flow ($\dot{V}$) falls below 0.1 L/S or the change in PCO_2 between successive measurement samples becomes less than 1 mmHg.

This criterion function and these end-tidal pointers have been chosen, in the light of accummulated experience, to cope with as many variations as possible in the breathing pattern of untrained subjects. It has proved to be fairly successful in this respect.

The CO_2 gas transport model equations developed in Chapter 2 can be summarised as follows :

$$V_A \frac{dP_A}{dt} = S\dot{V}(P_I^* - P_A) + \dot{Q}\left[b\,(P_{TC} - P_A) + A_{INT} \right] \text{ const.} \qquad 3.8$$

$$b\,V_{TC}\,\frac{dP_{TC}}{dt} = \dot{M} - \dot{Q}\left[\,b\,(P_{TC} - P_A) + A_{INT}\,\right] \qquad 3.9$$

$$S = \begin{cases} 1 - \text{if } \dot{V} > 0 \\ 0 - \text{otherwise} \end{cases} \qquad 3.10$$

$$P_I^* = \begin{cases} P_D - \text{if } \int \dot{V}\,dt < V_D \text{ and } \dot{V} > 0 \\ P_I - \text{otherwise} \end{cases} \qquad 3.11$$

In the above equations $\dot{Q}$ is the pulmonary blood flow or cardiac output, $\dot{M}$ the metabolic CO_2 production rate and V_{TC} the "effective" tissue volume, (see equation 2.41). V_A is the CO_2 lung volume which is made up of a time varying component and fixed component (FRC) as defined by equation 2.29. Recall that the FRC will in turn contain an additional volume contribution from the gas dissolved in lung tissue. 'b' is the slope of the CO_2 dissociation curve and is a function of the subjects measured Hb concentration as given by equation 2.16. A_{INT} is the difference between the mixed venous and arterial CO_2 dissociation curve intercepts and const is a gas laws scaling factor (see equation 2.24). P_I^* the model input, differs depending on the phase of the breath. In the first phase of inspiration (i.e. whilst the inspired volume is still less than the deadspace V_D) P_I^* is taken as the flow weighted mean of the gas notionally remaining in the deadspace at the end of the previous expiration. The formulae defining this are, equations 2.33 and 2.34 of Chapter 2. The input the model 'sees' in the later part of inspiration (i.e. where the inspired volume is greater than the dead space) has until recently been the instantaneous inspired PCO_2 as measured at the mouth (see 228). More recently, however, it has been realised that this does not properly take account of the transport delay through the dead space. For most breaths, where inspired PCO_2 within a breath

was constant, this inconsistency would not matter. However, during changes in input (e.g. during a switch from breathing air to 7% CO_2) this would result in the model 'seeing' the change in inspired PCO_2 before the actual lungs did. The data processing programme PRODAT (see next section) was therefore changed to 'retard' the PCO_2 data values by one dead space during this phase of inspiration to circumvent this problem.

In summary, the above equations contain the following model parameters. Firstly, those quantities entering directly into the above equations i.e. $\dot{Q}$, $V_A(O)$, $\dot{M}$, V_{TC} and A_{INT} . Secondly, those entering into the equations implicitly, i.e. Hb the blood haemoglobin concentration, V_D the anatomical dead space volume and finally P_A (O) and $P_{TC}(O)$ the initial partial pressures in the alveolar and tissue compartments respectively at time t = 0. Values also have to be assigned to these latter quantities.

Of the above parameters A_{INT} can be taken as fixed at 0.0129, Hb and V_D can be measured by standard respiratory laboratory techniques, and $P_A(O)$ can be measured directly from the experimental input/output data used by the method.

In earlier work V_{TC} was fixed a priori at the large value of 40 L. However, as the concept of the 'fast CO_2 tissue space' (see Chapter 2, section 2.7) unfolded this was felt to be inappropriate and V_{TC} was reintroduced as a parameter.

To calculate $P_{TC}(O)$ it is assumed that at time t = 0, the tissue compartment is in a steady state, i.e.

$$\frac{d P_{TC}}{dt} = 0 \qquad 3.12$$

substituting equation 3.12 in 3.9 therefore yields the following expression for $P_{TC}(O)$

$$P_{TC}(O) = P_A(O) + \frac{\dot{M}}{b\dot{Q}} - \frac{A_{INT}}{b} \qquad 3.13$$

In practice, however, due to the long time constant of the tissue compartment, it has been found beneficial to use a longer term average of P_A in equation 3.13 for $P_{TC}(O)$ in order to avoid possible inaccuracies due to short term fluctuations in P_A. Thus equation 3.13 is replaced by

$$P_{TC}(O) = P_{ABAR} + \frac{\dot{M}}{b\dot{Q}} - \frac{A_{INT}}{b} \qquad 3.14$$

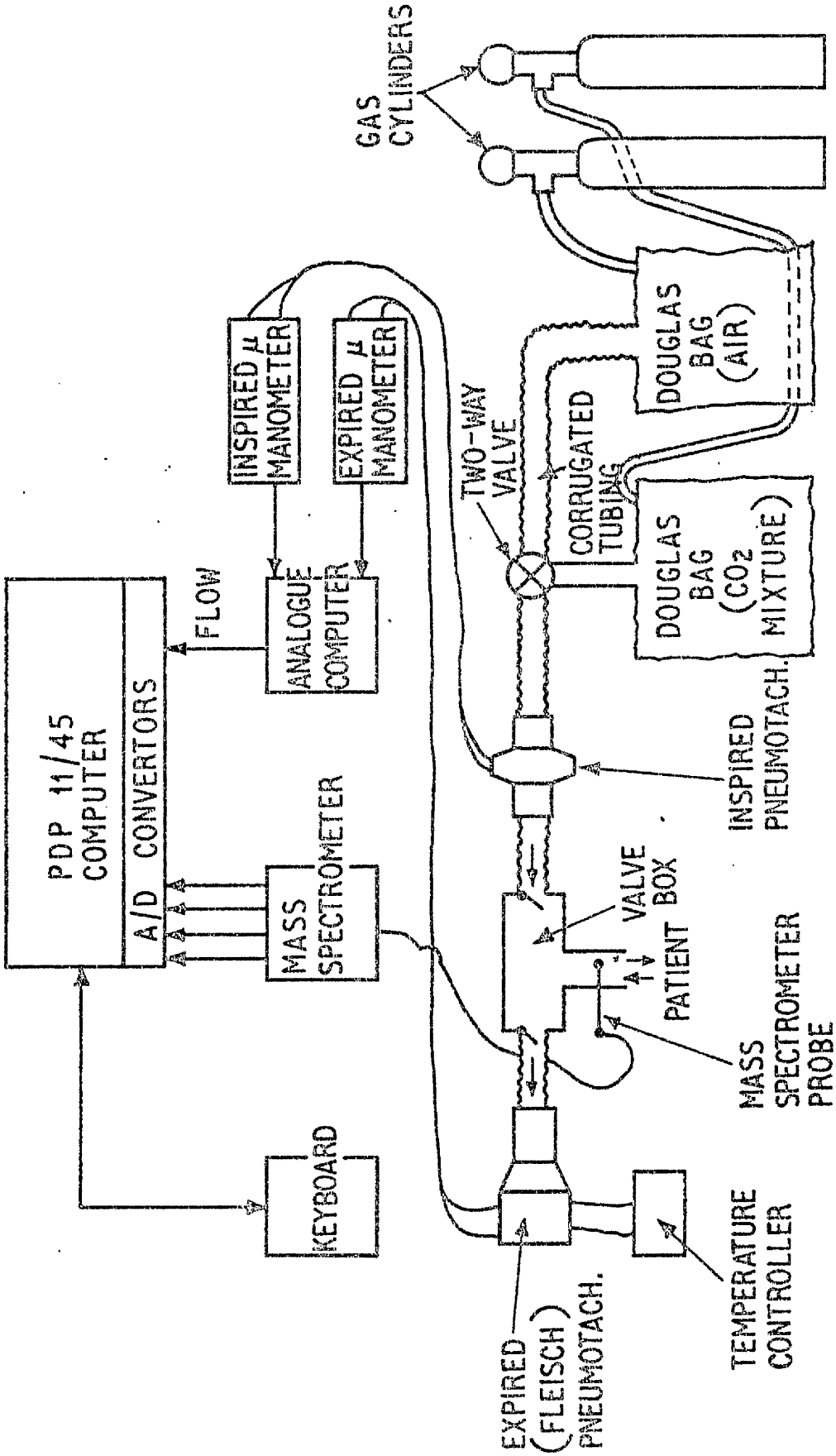
where $P_{ABAR} \neq P_A(O)$. This manner in which P_{ABAR} and $P_A(O)$ are deduced from the actual experimental data is discussed in the next section. Thus, assuming an initial steady state in the tissue compartment a value can be assigned to $P_{TC}(O)$ if $\dot{M}$, $\dot{Q}$, $P_A(O)$ and P_{ABAR} are fixed. Although the assumption is relaxed in subsequent chapters, in this chapter we shall use equation 3.14 to obtain $P_{TC}(O)$. The parameter estimation problem which remains, therefore, is to estimate the four parameters $\dot{Q}$, V_A, $\dot{M}$ and V_{TC}. Attempts to estimate additionally b and A_{INT} consistently failed due to numerical difficulties in the function minimisation programmes. The precise cause of this difficulty was not completely understood at this stage, although it was felt to be inexorably tied up with non uniqueness of the extended parameter set.

3.4 Experimental Rig and Data Processing

The on-line data acquisition system which has been used in the work described in this thesis is depicted diagrammatically in Figure 3.1. Photographs of the actual apparatus itself are shown in Figure 3.2. The author has not been directly concerned in the design and construction of this system. Nevertheless, for continuity purposes it is worthwhile briefly to summarise some aspects of the apparatus below. This system is described in more detail in (228, 234).

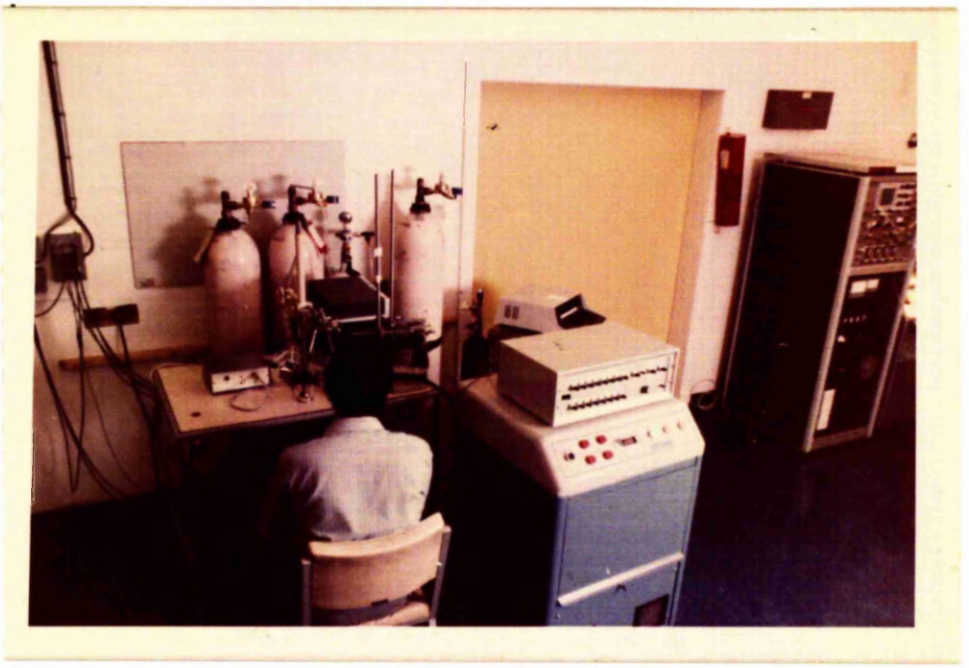
The potential subject, who is wearing noseclips, attaches himself to the rig using a standard rubber mouthpiece and breathes through a small dead space, low resistance, valve box. This valve box is such that it makes the subject breathe in through one port and out through another. A two way switch upstream from the valve input port allows the operator to change the subject's inspirate between room air and the stimulus mixture as dictated by the particular respiratory experiment. This set up forms a 'closed system' and enables the subject's ventilation and inspired and expired gas concentrations to be measured using the appropriate transducers.

The inspired and expired gas flow rates are measured separately by means of pneumotachometers. Until recently, expired flow has been measured using an ordinary pneumotach (this was in fact the system used in the experiments to be described later in this chapter). The nominal flow values so obtained are corrected in subsequent data processing to give overall ventilation balance over the duration of the test. This method is not particularly accurate, due to the possibility of water vapour in the expirate condensing in the flowmeter and causing a drift in calibration during the test. In later experiments, therefore, (i.e. those described in Chapter 7) this difficulty has been avoided by using a heated Fleish pneumotach to measure



EXPERIMENTAL RIG

FIGURE 3.1



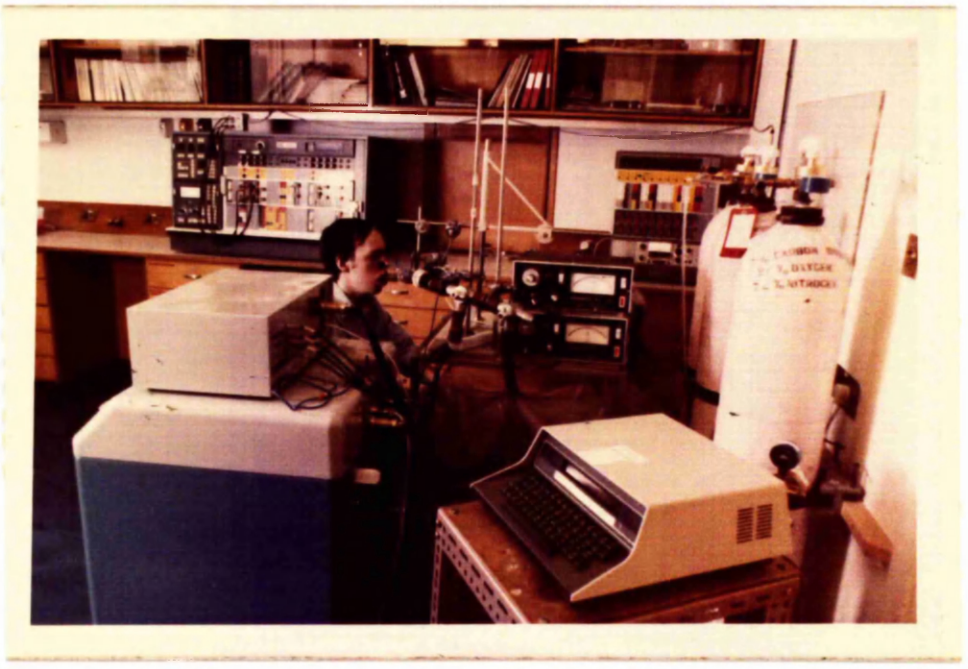


FIGURE 3·2

expired flow. A further recent improvement in the flow measurement has taken the form of a modification to the computer data collection programme to correct flow values for the differences in viscosity of the actual gas passing through the pneumotach and that of the gas used to calibrate the device (284).

The voltage outputs from the two micromanometers associated with the pneumotachometers are summed electronically using a small analogue computer before being fed to the PDP 11/45 computer system through the A - D interface.

Continuous measurements of a subject's gas concentration are made using a respiratory mass spectrometer. In earlier experiments (i.e. those described in this chapter) a Centronics MGA 7 type quadrupole device was used, but more recently the new Centronics MGA 100 mass spectrometer has been used (see photograph). The sampling probe for the mass spectrometer is placed proximal to the subject's lips. There is thus a transport delay inherent in this measurement equal to the time taken by the signal to travel the distance along the sampling line between the probe and the mass spectrometer itself (typically 100 - 200 ms). The measurement of respiratory flow is virtually instantaneous by comparison. Therefore, it is necessary to delay the flow signal to synchronise all the measured data. This is achieved by the data collection software. As we have seen in Chapter 2, in the application of dynamic models the partial pressure measurements for the gases being studied are required at BTPS conditions. It would appear simple to compute these quantities from the gas partial pressures, as measured at the mouth (e.g. P_{m_X}), by also measuring water vapour pressure at the mouth ($P_m H_2O$) directly and using the following formula :

$$P_{BTPS\,x} = P_{m_x} \cdot \frac{(B - 47)}{(B - P_m H_2O)} \quad (\text{mm Hg}) \qquad 3.15$$

However, due to certain technical difficulties (see Fowler (121)) this method is inaccurate.

In order to avert the problem with directly measuring water vapour, a method described by Davies et al (79) is used. This necessitates measuring the partial pressures of all the component gases in the total gas mixture to allow the fractional dry gas concentration of a particular gas under study to be obtained.

Having obtained F_x then the required P_x at conditions of full saturation with water vapour is obtained using

$$P_x = F_x (B - 47) \qquad (\text{mm Hg}) \qquad 3.16$$

Thus, in summary we see that for the applications involving dynamic models to be described in this chapter, it is necessary for the computer to acquire 5 channels of data via the A/D's viz flow, P_{N_2} , P_{CO_2} , P_{O_2} and P_{AR} . It now remains to describe the software steps involved in capturing this data and producing from it a file in a suitable format for use in the parameter estimation techniques discussed in the previous section. This software system consists of two parts :-

(1) the data logging programme

(2) the data processing programme.

The data logging programme which itself consists of four separate phases, will be discussed first.

In the first phase of the programme, prior to any data logging, using the keyboard an interactive dialog is set up between the computer and experimenter which allows information relevant to the forthcoming experiment to be input.

That is the datafile name, barometric pressure, temperature, mass spectrometer delay, length of experiment and sampling frequency (max 50Hz).

The next phase of the programme is essentially a calibration phase. In it the computer calculates the average voltage obtained over 500 scans of each A/D input channel when first a zero gas (i.e. one containing no trace of the gases under study - in this case Helium was used) and then a calibrate mixture (i.e. certain preknown fractions of the gases under study) was being sampled by the mass spectrometer. These averages allow the computer to associate voltages obtained on a given A/D channel with a corresponding flow or partial pressure in the subsequent experimental phase.

The third phase of the programme consists of data logging proper. During this procedure, normalised sampled data is stored on a temporary disc file at the rate and for the time specified in the earlier phase of the programme. Provision is also made during this experimental phase for the operator to communicate to the software the sample number when the gas stimulus mixture is first switched in by pressing the <CR> key on the keyboard at this time. This information is required by the later data processing programme. After the experiment is completed, the data residing in the temporary disc file is converted to physiological units (ATPD values) and scaled into integer form (to reduce storage requirements) for permanent storage on a file on magnetic tape. At this stage all input channels are synchronised by correcting for the mass spectrometer delay as discussed earlier. Also, an initial header record is added to the permanent file containing details associated with the stored data (e.g. barometric pressure, temperature, sampling rate, switch sample, etc.). The data, as generated at this stage from the logging programme, is liable to be noisy. That is, the flow signal will be corrupted

by mechanical valve flutter and the PCO_2 signal by cardiogenic oscillations, both of which constitute, in this context, high frequency noise. It is also inevitable that the subject (especially if unaccustomed to respiratory experiments) will have coughed or swallowed at some stage in the experiment. These responses represent departures from the normal breathing rhythm and thus, if left unmodified, will cause complications in the interpretation of the data record in the subsequent analysis. Thus, the data output from the logging programme requires further filtering and application specific processing, to render it suitable for use with the CO_2 model based parameter estimation software. This is done by the processing programme PRODAT.

In the first part of PRODAT, both the flow and PCO_2 channels are filtered using a simple low pass filter (cut-off frequency one quarter of the sampling frequency).

The sample numbers corresponding to the beginning and end of inspiration/expiration for each breath are then identified. This is done using a heuristic algorithm which searches initially for a threshold value (0.15 L/S) in the flow signal and then backwards from this for the nearest preceeding point at which a zero cross-over occurs. This obviates difficulties caused by noise in the flow signal which would lead to spurious breaths being recognised, if only zero crossovers themselves were identified. This being done, the inspired and expired volume of each breath are then computed. At this stage the programme corrects for consecutive inspiration (expiration) (usually a result of swallowing or coughing) by changing these to one inspiration (expiration) with resultant volume equal to the sum of the two previous ones, and renumbering all the breath numbers appropriately. In this first part of the programme it is also ensured that the "standard experiment" which will ultimately be presented to the estimation software, begins with a complete inspiration and

ends with a complete expiration. In the results presented in this chapter this "standard experiment" is of $1\frac{1}{2}$ minutes duration and takes the form of 40 seconds of air breathing followed by 80 seconds breathing 5 - 7% CO_2.

In the second part of the programme, the quantities $P_{A(O)}$ and P_{ABAR} are calculated, which are used in determining the model initial conditions $P_{A(O)}$ and $P_{TC(O)}$ (see previous section). Although various formulae have been used for computing, these quantities in the past, the one used at present is as follows. $P_{A(O)}$ is taken as the maximum end-tidal PCO_2 value for the expiration preceeding the start of the standard experiment. P_{ABAR}, however, which represents a longer term average of $P_{A(O)}$ for use in the calculation of $P_{TC(O)}$ (see equation 3.14) is taken as the mean of the last three samples at the end of expiration, additionally averaged over all the breaths in the first air breathing phase of the experiment. The rationale behind this is discussed in the previous section.

An estimate of the subject's anatomical dead space is required at various stages in the analysis procedure (i.e. to retard the CO_2 channel by one dead space, and to define properly the model and data E/T regions). Until recently, this has been obtained by a separate test involving a single breath of O_2 and analysis of the resultant expired N_2 curve (118). However, more recently a side benefit of using improved hardware to measure expired flow is that it makes it possible to calculate accurate anatomical dead space measurements from the CO_2 data during the initial air breathing phase of the experiment. This obviously has the advantage of cutting out a step (which can be time consuming and cumbersome) in the experimental procedure. This calculation is now done at this point in the PRODAT programme and this is the value now used for V_D in the subsequent analysis.

Next, a separate volume channel is created for use in the estimation

software by integrating the flow channel using the trapezoidal rule and all the data corrected to BTPS as required. After this, the CO_2 channel is retarded to correct for the buffering effect of the dead space as discussed in the previous section and then the viscosity correction to the flow channel is carried out.

Finally, the modified data in the header block is output to a new file in a standard format, now ready for use with the parameter estimation programmes.

3.5 Results of the Early Validation Studies

In early 1977 the non invasive cardiac output method was assessed by carrying out repeated simultaneous measurements by this method and by a dye-dilution method in a number of subjects at Glasgow Royal Infirmary. These subjects were patients with hypertension but with otherwise normal lung function. It was intended to make use of the cardiac output information obtained from these patients in the management of their hypertension.

The standardised experimental procedure adopted in these studies was as follows.

The subject had the venous and arterial catheters necessary for the dye measurements inserted on arrival. The comparative measurements were then carried out with the subject in the supine position and at rest. After insertion of the mouthpiece, three minutes were allowed for the subject to calm down and for the breathing pattern to stabilise. The gas exchange measurements were then started, the total duration of the data collection period being two minutes: 40 secs. air breathing and 80 secs. breathing 5 or 7% CO_2. The dye dilution measurement, which lasted about 30 secs. was started simultaneously with the CO_2 breathing phase. A minimum of 10 minutes was allowed between repeated gas exchange measurements to allow any possible

effect of CO_2 on cardiac output to diminish (110,204b). Generally it was aimed to collect four sets of comparative measurements per subject, but due to experimental difficulties (invariably with the dye procedure !) this was not always possible. Measurement of the subject's anatomical dead space (118) was either carried out on arrival or at the end of the series of comparative measurements.

In total 51 pairs of simultaneous measurements were obtained from a set of 16 patients. However, the function minimisation procedure failed to find a minimum in 3 sets of data, therefore, leaving only 48 valid comparative results on which to base conclusions. The parameter values obtained from the model-based method and the corresponding dye-dilution results are detailed in Table 3.3. From this it can be seen that the parameter values obtained from the estimation procedure are physiologically meaningful.

The cardiac output estimates obtained from the model are in good agreement with those obtained by the dye-dilution technique.

The estimates of metabolic production obtained by parameter estimation also agreed closely with those obtained independently on the basis of steady state analysis of overall gas uptake.

The estimates for tissue volume are of the correct order of magnitude as compared to published data (117) and the values obtained can be related to the extra cellular fluid 'fast space' for carbon dioxide (see Chapter 2, section 2.7).

The estimated carbon dioxide lung volumes obtained originally appeared rather low when compared with the FRC's (Fixed Residual Capacity) of the patients as measured by inert gas washout. This was rather worrying for a time, since the estimated CO_2 lung volume is notionally an equivalent

TABLE 3.3

VALIDATION RESULTS USING

4 PARAMETER MODEL

Subject	Data file	$\dot{Q}$ dye	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}
J M^{c}E	VAL041	5.96	6.45	1.85	0.265	7.18
7% CO_2, V_D = 0.83	2	6.18	6.36	1.73	0.237	9.21
Hb = 14.15, FRC = 4.29	3	5.60	6.29	1.92	0.262	11.8
	4	5.10	5.87	1.62	0.213	7.7
J M^{c}C	VAL051	6.57	6.84	2.54	0.300	13.1
5% CO_2, V_D = 0.156	2	5.30	5.58	2.66	0.295	8.76
Hb = 14.9, FRC = 3.47	3	5.13	7.10	3.05	0.334	10.1
IF	VAL072	5.03	6.89	1.36	0.244	4.87
5% CO_2, V_D = .076	4	4.99	6.50	1.39	0.218	4.04
Hb = 13.5, FRC = 3.18						
JC.	VAL081	5.13	5.16	0.96	0.185	5.15
7/5% CO_2, V_D = 0.139	4	5.63	5.94	2.34	0.208	6.66
Hb = 14.65, FRC = 2.66	5	5.37	5.97	0.98	0.207	4.94
KM^c	VAL101	9.44	8.23	2.22	0.310	10.9
7% CO_2, V_D = 0.178	2	9.55	7.66	1.58	0.277	7.23
Hb = 14.55, FRC = 2.78	3	8.54	7.40	1.92	0.276	8.35
	4	8.43	7.38	1.91	0.328	10.4
JK	VAL111	6.72	5.63	2.66	0.272	7.49
5% CO_2, V_D = 0.176	2	5.57	5.44	2.26	0.277	10.2
Hb = 15.7, FRC = 3.29	3	6.11	7.79	2.39	0.302	9.11
	4	5.93	8.58	1.40	0.258	6.02
RC	VAL122	4.42	4.21	1.63	0.210	4.59
7% CO_2, V_D = 0.132	3	3.95	—			
HB = 13.35, FRC = 3.01	4	4.02	3.13	2.03	0.187	2.87
	5	4.20	4.50	1.80	0.237	4.46
JA	VAL141	6.44	7.30	2.18	0.361	8.94
7% CO_2, V_D = 0.139	2	5.98	6.34	1.42	0.266	6.83
Hb = 15.45, FRC = 2.60	3	7.00	—			
	4	6.55	5.86	1.84	0.264	5.38

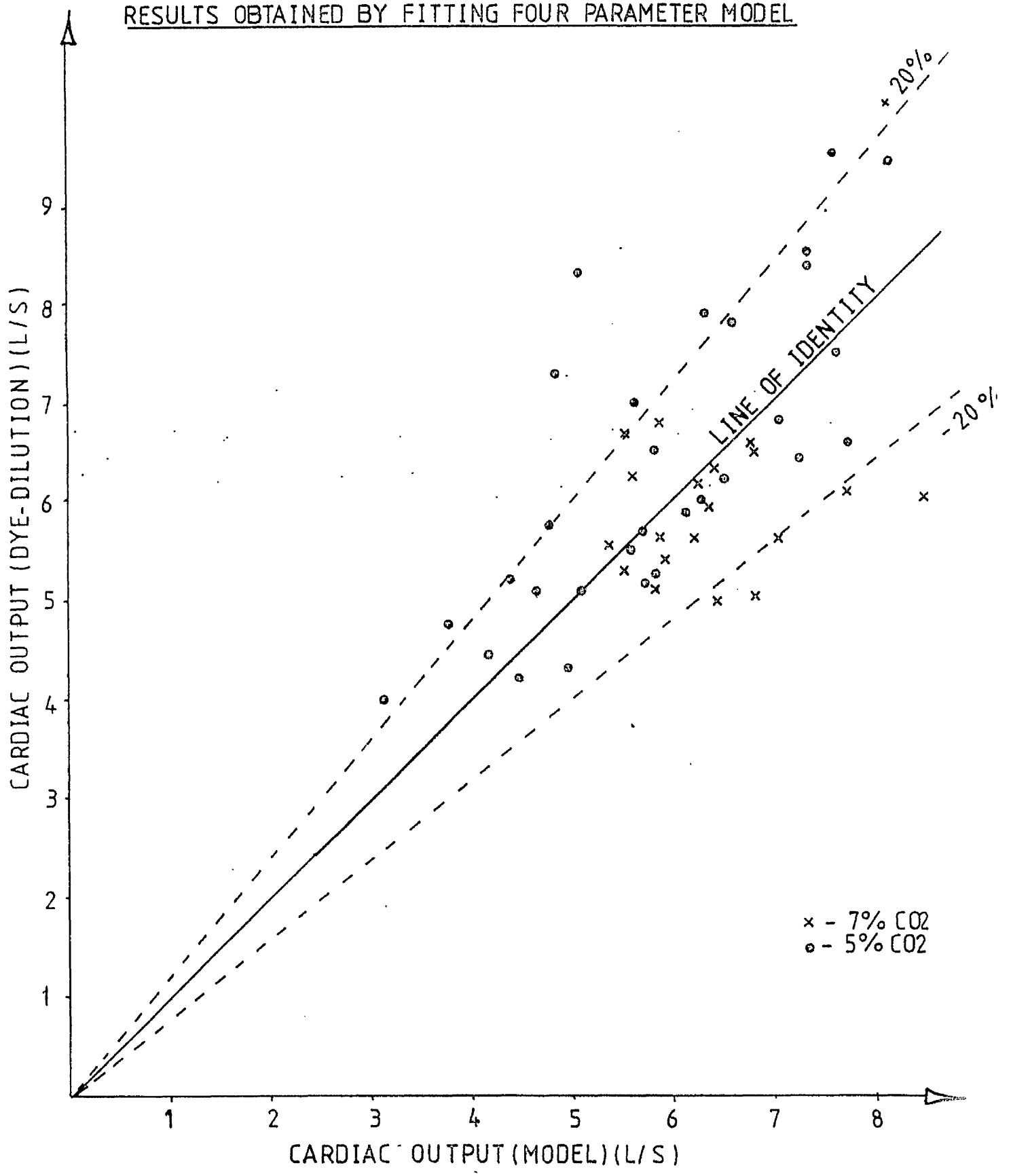
TABLE 3.3 continued .....

Subject	Data file	$\dot{Q}$ dye	$\dot{Q}$	VA	$\dot{M}$	V_{TC}
SD.	VAL161	6.48	6.93	2.36	0.261	5.93
5% CO_2 , V_D = 0.156	2	6.79	5.94	1.29	0.209	3.73
Hb = 15.25, FRC = 3.10	3	6.26	5.68	3.66	0.259	7.73
	4	6.35	6.48	2.73	0.275	7.47
JS.	VAL172	8.29	5.13	1.68	0.242	2.31
5% CO_2, V_D = 0.171	3	7.85	6.71	3.43	0.288	6.62
Hb = 16.85, FRC = 3.90	4	7.35	4.92	1.48	0.237	4.11
GM.	VAL181	5.11	4.73	1.58	0.234	4.11
7% CO_2, V_D = 0.228	3	4.28	4.98	1.73	0.255	5.34
Hb = 14.4, FRC = 4.68	4	5.26	4.46	1.41	0.234	4.00
JF.	VAL191	4.82	3.78	1.26	0.182	3.96
7% CO_2, V_D = 0.159						
Hb = 14.25, FRC = 4.29						
CR.	VAL203	7.87	6.40	1.65	0.259	5.10
7% CO_2, V_D = 0.178						
Hb = 15.65, FRC = 3.19						
DB.	VAL221	5.50	5.70	2.16	0.294	9.11
7% CO_2 , V_D = 0.143	2	5.20	5.78	2.03	0.263	6.08
Hb = 15.85, FRC = 3.08	3	5.30	5.94	1.81	0.255	5.53
	4	5.70	5.76	1.86	0.247	5.24
DH.	VAL231	7.50	7.71	2.99	0.398	12.4
7% CO_2 , V_D = 0.137	2	6.30	6.64	1.82	0.212	5.69
Hb = 14.3, FRC =	3	6.60	7.78	3.26	0.357	12.9
AR.	VAL251	6.76	6.46	1.65	0.239	6.57
7% CO_2, V_D = 0.171	2	5.90	6.19	1.45	0.211	4.92
Hb = 15.2, FRC = 2.56	3	5.75	4.79	1.57	0.236	5.73
	4	5.74	—			

lung volume including also the equivalent of gas volume dissolved in lung tissue, and therefore, should be greater than FRC. This worry was cleared up, however, when it was realised that the FRC's had been measured while sitting, whilst our measured CO_2 lung volumes reflected results obtained when the patients were supine. One would expect the lung volumes to be different in these two positions as the ventilation flow distributions in the lung are different in each case (294). Some experimentation quickly confirmed that FRC's in a given subject are smaller in the supine position as opposed to the sitting position, thus clearing up the anomaly in the lung volume results. We will now concentrate further on the details of the comparative measurements of cardiac output.

In Figure 3.3 the individual results, as obtained by the two different methods, are plotted. These results are further summarised statistically in Table 3.4. Figure 3.3 shows that most of our results (34/48) lie within $\pm$ 20% of the dye-dilution values. This is about the same fractional success rate as that reported by Homer and Denysyk (155) in the best previously published study to estimate cardiac output by modelling techniques (27 out of 36). Recall, however, from the discussion in Section 3.2 that the technique of Homer and Denysyk uses endo-tracheal sampling, i.e. it is invasive. It is, therefore, noteworthy that, in spite of the reduction in available information which our non-invasive technique imposes, we have been able to obtain results as good as those obtained using a similar but invasive technique.

Table 3.4 shows the average agreement between dye and computed values is fairly good. The mean difference of the 48 pairs of values is 0.02 L/M (although the standard deviation of the mean difference is 1.12 L/M). However, the "plum pudding" shape of Figure 3.3 shows there is considerable discrepancy between computer-generated and dye results in some cases. This is also



VALIDATION DATA

FIGURE 3·3

TABLE 3.4

STATISTICAL SUMMARY OF COMPARATIVE MEASUREMENTS OF CARDIAC OUTPUT USING 4 PARAMETER MODEL

Files	Corr. coeff.	Reg. coeff.	Intercept	Mean Diff. (comp-dye) L/M	S.D. Diff. (comp-dye) L/M	P *
All (48)	0.59	0.66	2.09	0.02	1.12	NS
7% CO_2 (27)	0.86	0.98	0.36	0.24	0.80	< 0.2

* P values obtained from paired Student's t-test (two-tailed).

36/48 paired observations within $\pm$ 20% of line of identity.

mean reproducibility (dye) - 6.8%

mean reproducibility (all comp) - 10.6%

mean reproducibility (7% CO_2) - 9.7%

reflected in the low correlation coefficients in Table 3.4.

Comparing our results with those published by other authors for validation studies in resting subjects (see Table 3.2), we can see our results are not as good as those of Franciosa et al (122) (r = 0.97) using the Indirect Fick. However, our results using 7% CO_2 are better than those recently reported by Reybrouck et al (243) who like Franciosa et al, also use an Indirect Fick method.

In assessing the reproducibility of measurement of cardiac output by our new non-invasive method, it must be said that the results are rather disappointing. Examination of the results in Table 3.3 shows that in a given subject, our method gives a greater spread of values than that of the dye-dilution method. This spread is reflected in the average coefficients of variation for the two methods: 6.8% for dye dilution, 10.6% for our method, overall, 9.7% for the 7% CO_2 experiments. (Coefficient of variation (CV) = $\frac{\text{Standard deviation}}{\text{mean}}$, the lower the CV, the better the reproducibility). We can see how these results compare with those of other published investigations at rest by examining Table 3.1. Here we see that although our reproducibility results are better than those of Ferguson et (109) they do not compare with those of Franciosa et al (122) using Indirect Fick CO_2 rebreathing or other published results for dye dilution at rest.

In conclusion, these validation results would appear to indicate that although the overall accuracy of the new computer-based cardiac output method is quite good, in terms of variability it is necessary to improve the technique in order to create a sufficiently attractive clinical tool. The remainder of the work described in this thesis is directed towards this aim.

CHAPTER 4

STATISTICAL SYSTEM IDENTIFICATION AND ITS APPLICATION TO THE CARDIAC OUTPUT MEASUREMENT TECHNIQUE

4.1 Introduction

In Chapter 1 of this thesis the topic of time domain system identification was introduced. Chapter 3 may have tended to convey the idea that, once an 'ad hoc' criterion to define goodness of fit between model and data is proposed, system identification reduces in essence to a problem of mechanistic function minimisation. In fact, prior to the involvement of the author in the project, the problem had been formulated precisely in this manner.

With the disappointing nature of the results detailed in Chapter 3, it became apparent that attacking things in this way was not entirely appropriate. As pointed out in much of the literature, identification is essentially a statistical procedure (43, 62, 63, 220).

Most criterion functions used for model system comparison are implicit functions of the observations. These observations are corrupted by noise, which is random in nature. This implies the estimates themselves will also be subject to randomness in the sense that one set of measured data, under seemingly identical experimental conditions, will be unlikely to produce the same estimate as another data set. This necessitates a probabilistic analysis.

It transpires that the criterion suggested for model-data comparison in Chapter 3 can be given a useful statistical interpretation when viewed in this light. By casting the problem in this probabilistic framework, important questions can be posed which allow one to assess the adequacy of the estimated model.

(1) How well defined are the parameters in parameter space ? (i.e. what are their associated variances ? Are they correlated ?)

(2) What criterion function would allow us to produce the "best" estimates ? (In the sense of being unbiased and having smallest variance.)

(3) Do our a priori assumptions about model order appear to be correct on the basis of the achieved fit ?

(4) Could an experiment be devised which would allow us to produce "better" estimates ?

It was felt the answers to the above questions and connected ones provided the main key to understanding the relatively poor results presented in the previous chapter and, in fact, the search for these answers formed the main goal of the work described in this thesis. Questions 1 - 3 are investigated in the succeeding sections of this chapter, while Question 4 is discussed in Chapter 7.

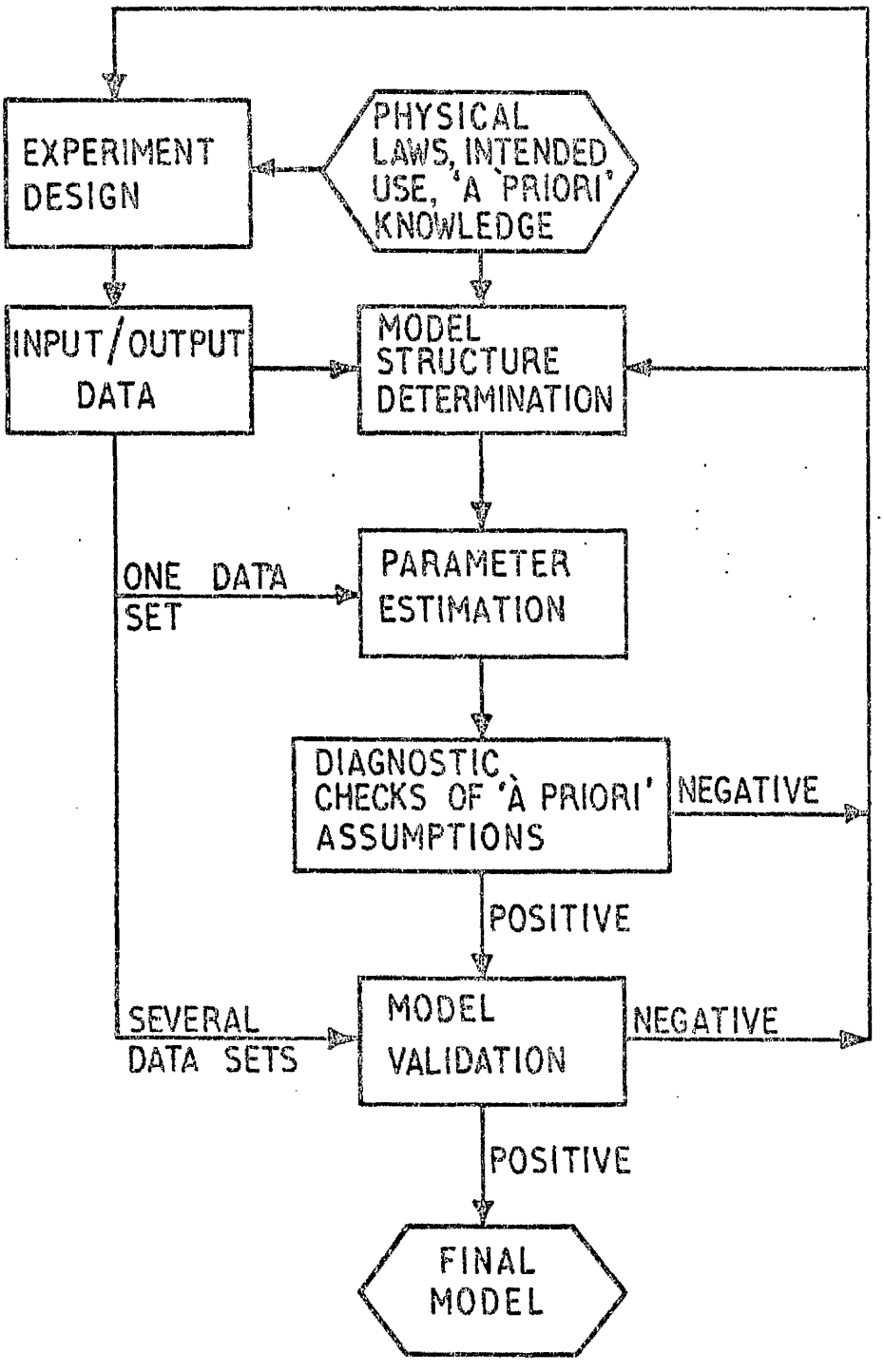
Once the answers to these questions have been found, this allows us to re-examine the original assumptions inherent in the model and the form of experiment and suggest modifications where necessary. This approach views the problem as an iterative procedure, rather than just a 'one-shot' process. The new methodology is summarised in Figure 4.1.

4.2 Statistical Background

An estimator of an unknown parameter vector β is simply an algorithm which takes measured data (Y_D say) and produces an estimate $\hat{\beta}$. An estimator, being a function of a random sample of measurements, is a random variable. The estimate which results is a particular realisation of this random variable.

Clearly, a good estimator should be such that it produces estimates $\hat{\beta}$ 'close' to the true vector β . This leads to the concept of an unbiased estimator. An estimator is said to be unbiased if

$$E (\hat{\beta}) = \beta \qquad 4.1$$



THE IDENTIFICATION PROBLEM

FIGURE 4·1

Here $E(\hat{\beta})$ denotes the expected value of $\hat{\beta}$. (A particular value of an unbiased estimator is known as an unbiased estimate). The above property may be true of the estimator for any number 'm' of observations or may be true only in the limit as 'm' tends to infinity. In the latter case, the estimator is designated as being asymtotically unbiased. The covariance matrix of an unbiased estimator $\hat{\beta}$ of the parameter vector β is

$$\text{cov}\ (\hat{\beta}) = E\left\{(\hat{\beta} - \beta)(\hat{\beta} - \beta)^T\right\} \qquad 4.2$$

The diagonal elements of cov $(\hat{\beta})$ represent the variances of the parameters as calculated in the normal scalar case and the off-diagonal elements represent the covariances between the respective parameters.

An obvious requirement for a 'best' estimator is that it should produce unbiased estimates. In addition, it should produce a parameter estimate covariance matrix which is smaller in some sense than that produced by other unbiased estimators. Such an estimator is known as a minimum variance unbiased estimator (MVUE).

It is not often feasible to establish the existence of such estimators. In practice, it is usually enough to show that the estimator provides a covariance matrix which approaches what can be shown to be the lower bound for all unbiased estimators. This is given by the Cramer-Rao inequality (261)

$$\text{cov}\ (\hat{\beta}) \geqslant M(\beta)^{-1} \qquad 4.3$$

where

$$M(\beta) = E\left\{\left[\partial \log \frac{\text{prob}}{\partial \beta}\ (Y_D / \beta)\right]\left[\partial \log \frac{\text{prob}}{\partial \beta}\ (Y_D / \beta)\right]^T\right\} \qquad 4.4$$

$M(\beta)$ is known as Fishers Information Matrix. It can be thought of as providing a measure of the amount of information about the parameter vector β available in the observations Y_D . The inverse of this is known as the Cramer-Rao Lower Bound and an estimator which achieves this lower bound

is said to be efficient.

Prob (Y_D / β) in equation 4.4 is the conditional density function of the actual observed data samples. This is called the likelihood function

$$L (Y_D , \beta) = \text{prob} (Y_D / \beta) \qquad 4.5$$

An estimator which maximises this is called a maximum likelihood estimator. This is such that

$$\frac{\partial L (Y_D , \beta)}{\partial \beta} = 0 \qquad 4.6$$

This is equivalent to

$$\frac{\partial \log L}{\partial \beta} (Y_D , \beta) = 0 \qquad 4.7$$

since the logarithm function is monotonic. This latter criterion is more frequently used since log L is often much more convenient to compute than L alone.

The resultant estimate using this estimator can be thought of as that which makes the data samples Y_D which actually occurred, most likely.

Unfortunately, Maximum Likelihood estimates are not in general unbiased. However, they do possess certain desirable large sample properties under fairly weak conditions (261). The maximum likelihood estimator is, therefore, a fairly attractive one provided the estimates can be computed.

4.3 The Least Squares Estimator

The parameter estimation problem can be formulated conceptually around the process model in Figure 4.2 . It is required to estimate the values of the unknown parameter vector β from discrete observations Y_{Di} of the model output Y_{Mi} which is corrupted by additive noise, e_i . Using the notation

SAMPLED PROCESS MODEL WITH ADDITIVE NOISE

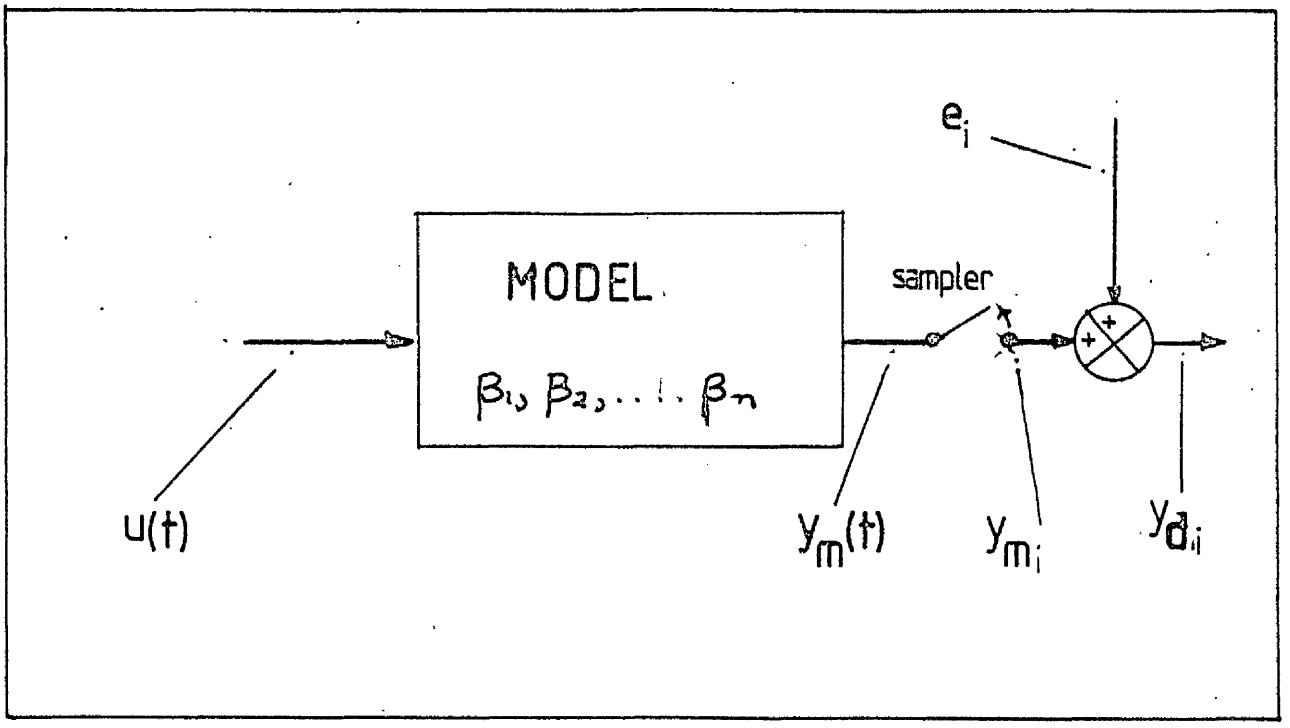


FIGURE 4·2

of regression analysis (93), we may write this model in the following vector-matrix form.

$$Y_D = Y_M + e \qquad 4.8$$

where

$$Y_M = X\beta \qquad 4.9$$

Y_D is an $m \times 1$ vector made up of the 'm' discrete observations, Y_M the vector of model outputs and e the vector of additive errors corresponding to these. X is an $m \times n$ sensitivity matrix made up of the sensitivities of the model output at the ' m ' discrete time instants to the ' n ' model parameters, i.e.

$$\underline{X} = \begin{bmatrix} \frac{\partial Y_{M_1}}{\partial \beta_1} & \cdots & \frac{\partial Y_{M_1}}{\partial \beta_n} \\ \frac{\partial Y_{M_2}}{\partial \beta_1} & & \\ \vdots & & \\ \frac{\partial Y_{M_m}}{\partial \beta_1} & \cdots & \frac{\partial Y_{M_m}}{\partial \beta_n} \end{bmatrix} \qquad 4.10$$

For a model linear in the parameters (as discussed in Chapter 1) X is independent of the parameter vector β in contrast to the case of a model non-linear in the parameters where X contains elements dependent on β. This has fundamental consequences in terms of the techniques used to compute the parameter estimate $\hat{\beta}$ as we shall see.

Note that the problem of estimating the parameters of the homogeneous CO_2 gas transport model described in the previous Chapter, can be interpreted in the form of equations 4.8 and 4.9 by interpreting Y_{Di} and Y_{Mi} as the flow-weighted means of the data and model output respectively for each breath. Thus, the 'ad hoc' criterion used for model/data comparison in the previous

Chapter can be viewed as an algorithm for minimising the sum of squares of the additive observation residuals, i.e.

$$\underset{\text{w.r.t. } \beta}{\text{Min.}} \; V(\beta) = \sum_{i=1}^{m} e_i^2 \quad \text{or} \quad e^T e \qquad 4.11$$

This criterion is in fact more widely known in a general context as the ordinary least squares (OLS) criterion. The criterion has been given historical prominence due to its mathematical tractibility and the fact that its validity does not depend on the nature of the additive noise statistics (as has been aptly illustrated in the previous chapter).

For a model linear in the parameters the solution to equation 4.11 can be given analytically by the so-called normal equations, i.e.

$$\hat{\beta}_{LS} = \left[X^T X \right]^{-1} X^T Y_D \qquad 4.12$$

If the model is non-linear in the parameters, using this equation to compute $\hat{\beta}_{LS}$ is no longer applicable since X is a function of β. In this situation the estimate must be computed iteratively using function minimisation methods. This important problem is extensively discussed in Chapter 5 and 6. However, it is important to note that in the non-linear case, equation 4.12 is a valid approximation for $\hat{\beta}$ provided this $\hat{\beta}$ is also used to compute X.

For theoretical examination of the properties of the OLS estimator we must assume some statistical properties for the additive noise. The following analysis, although only strictly valid for the case of a model linear in the parameters, can be extended to the non-linear case with due caution. Assume firstly the noise is zero-mean, i.e.

$$E(e) = 0 \qquad 4.13$$

and, furthermore, that X is non-stochastic.

Under these assumptions it can be shown that the least squares estimator

is unbiased. Taking expectations on both sides of equation 4.12 and applying 4.13 we get

$$E(\hat{\beta}_{LS}) = E(\beta) + E\left[(X^T X)^{-1} X^T\right] E\left[(e)\right] = \beta \qquad 4.14$$

The covariance matrix of the least squares estimator under these assumptions is

$$\text{cov}(\hat{\beta}_{LS}) = E\left\{\left([X^T X]^{-1} X^T e\right)\left([X^T X]^{-1} X^T e\right)^T\right\}$$

$$= \left[X^T X\right]^{-1} X^T N X \left[X^T X\right]^{-1} \qquad 4.15$$

N is defined as the covariance matrix of the additive noise.

$$N = E\left\{e\ e^T\right\} \qquad 4.16$$

However, this does not provide the minimum variance estimator unless it is also assumed the noise is uncorrelated and has constant variance σ^2, i.e.

$$N = \sigma^2 I \qquad 4.17$$

where I is the identity matrix. In this situation equation 4.15 reduces to

$$\text{cov}(\hat{\beta}_{LS}) = \sigma^2 \left[X^T X\right]^{-1} \qquad 4.18$$

which is the minimum covariance matrix of $\hat{\beta}$.

This inability to give minimum covariance estimates in the presence of correlated observation errors is an important deficiency of the ordinary least squares method. This problem is further pursued in Section 4, where a method is presented which overcomes this difficulty.

If in addition to the assumptions detailed above, the noise is also assumed to be governed by a Gaussian distribution of joint probability

$$\text{prob}(e\ ,\ \beta) = (2\pi\ \det N)^{-\frac{m}{2}}\ \exp\left\{-\tfrac{1}{2}\ e^T\ N^{-1}\ e\right\}$$

$$= (2\pi\sigma^2)^{-\frac{m}{2}}\ \exp\left\{-\tfrac{1}{2}\ e^T\ e\right\} \qquad 4.19$$

Then the ordinary least squares estimator coincides in this case with the maximum likelihood estimator. The log likelihood function for equation 4.19 is given by

$$\log\ L = -\ m \log 2\pi\sigma\ \ -\tfrac{1}{2}\ \frac{1}{\sigma^2}\ e^T e \qquad 4.20$$

Thus, it is evident that minimising $e^T e$, which is the least squares criterion, is equivalent to maximising the likelihood function.

Since the variance of the noise is seldom known a priori, a maximum likelihood estimate of this can also be obtained by differentiating equation 4.20 with respect to σ^2. This gives

$$-\frac{m}{\hat{\sigma}}\ +\ \frac{1}{\hat{\sigma}^3}\ e^T\ e\ \ \ \ = 0 \qquad 4.21$$

transforming we get

$$\hat{\sigma}^2\ =\ \frac{1}{m}\ e^T e \qquad 4.22$$

It can be shown, however, that this estimate is biased (158) and a better unbiased estimate is

$$\hat{\sigma}^2\ =\ \frac{1}{m-n}\ \ e^T e \qquad 4.23$$

Thus an estimate of the covariance matrix of the parameters based on the achieved fit is given by equation 4.18 with σ^2 replaced by $\hat{\sigma}^2$ as given by the above equation.

The inverse of $\text{cov}(\hat{\beta})$ describes an elliptical surface in parameter space, which is equivalent to that of the criterion function surface (as given by equation 4.11) to first order in the region of the minimum. The eigenvectors

of $X^T X$ define the axes of this elliptical surface and the size of its semi-axes are inversely proportional to the square root of the corresponding eigen-values (see Fig. 4.3).

From the cov ($\hat{\beta}$) matrix approximate confidence sets for the parameters may be constructed which describe plausible regions in which the parameters can be expected to lie to a given probability level (usually 95%). For a value of $\hat{\sigma}^2$ as given by equation 4.24, it is appropriate to base the confidence distances on the students t-distribution (126). This is given for e.g. the i^{th} parameter

$$\hat{\beta}_i \pm \hat{\sigma} \, \text{cov} (\hat{\beta})_{ii}^{\frac{1}{2}} \, t (m - n) \qquad 4.24$$

The students t distribution is tabulated for different levels of confidence as a function of degrees of freedom $m - n$. In fact, at the 95% confidence level for $m - n$ greater than about twenty the value of t is not greatly different from 2.0 and thus the above formula approximately reduces to

$$\hat{\beta}_i \pm 2 \, \hat{\sigma} \, \text{cov} (\hat{\beta}_{ii})^{\frac{1}{2}} \qquad 4.25$$

Note these confidence distances may be greatly in error for a model highly non-linear in the parameters since the confidence regions will be no longer approximately elliptical in this case. Beck and Arnold ((22) Ch. 7) advocate that alternative confidence regions (which may be asymetrical) based on the likelihood ratio be used in this situation.

To consider the overall fit, a convenient scalar measure of the size of an ' n ' dimensional ellipsoid is its volume, the square of which is proportional to the determinant of cov ($\hat{\beta}$) (220),

$$\text{vol} \propto \det (\text{cov} (\hat{\beta})) \qquad 4.26$$

Thus appropriate 95% confidence ellipsoids may be constructed based on this.

SURFACE DESCRIBED BY $\underset{\sim}{X}^T \underset{\sim}{X}$.

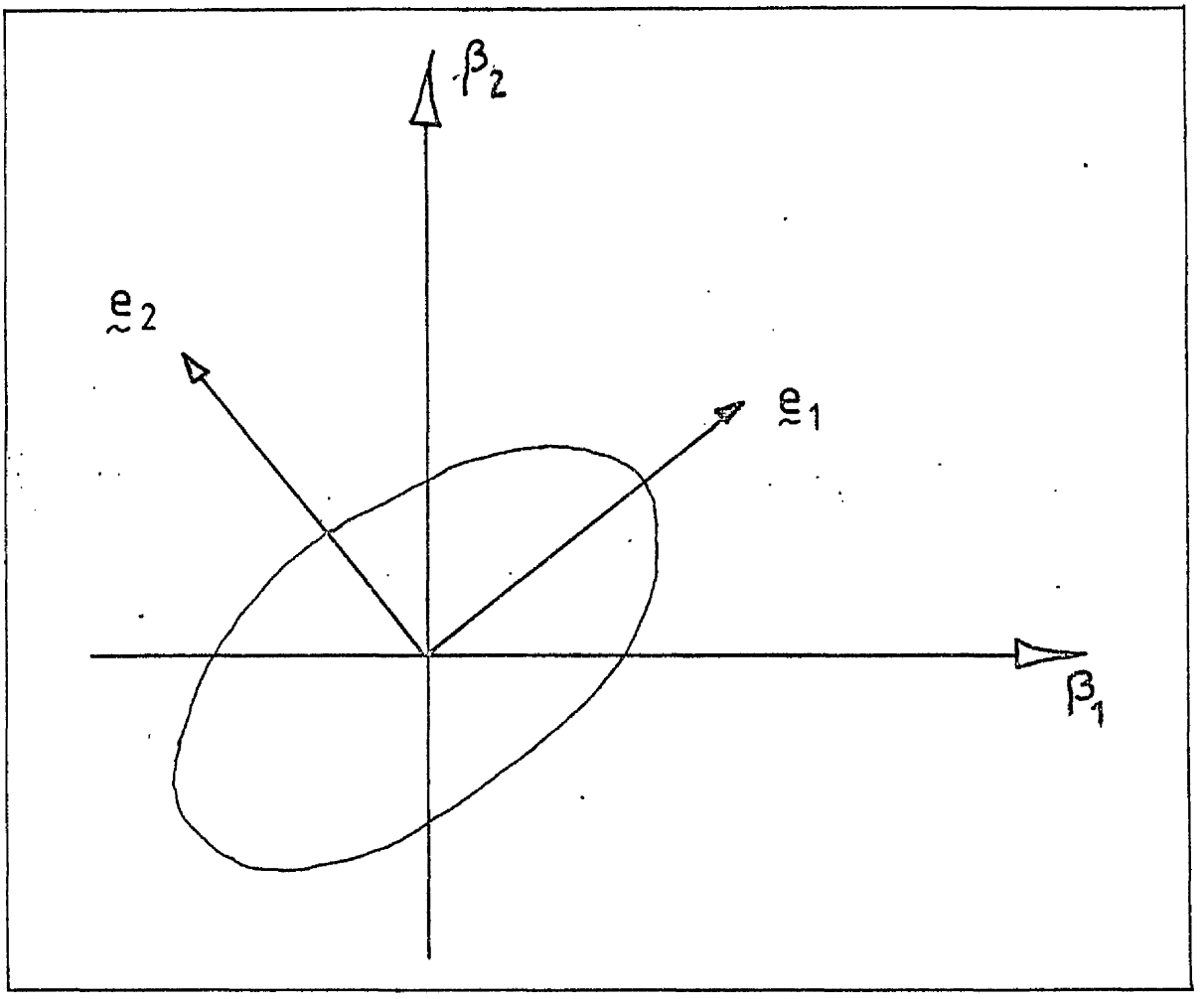


FIGURE 4·3

4.4 "Maximum Likelihood" Estimator

When the fitting errors (or in the terminology of regression analysis the residuals) are correlated, it has been shown in the previous section that the ordinary least squares approach does not produce minimum variance and maximum likelihood estimates.

Better estimators (in the sense of producing estimates with smaller variance) may be derived from a knowledge of the parameters of the noise or more precisely, its covariance matrix. Unfortunately this is not generally known a priori.

By utilising a more general form of noise model than that of ordinary least squares, the parameters of the noise model may then be estimated in addition to the deterministic model parameters as part of the overall estimation process. The penalty that must be paid for this is, of course, the increased dimensionality of the problem. However, the resultant "maximum likelihood" estimator (11) yields minimum variance estimates under less stringent statistical assumptions on the noise than the ordinary least squares method requires to produce minimum variance estimates. A suitable form of model to use to represent the correlated noise e is the following discrete time model.

$$e_t = \frac{\left[1 + b_1 z^{-1} + b_2 z^{-2} + b_n z^{-n}\right]}{\left[1 + a_1 z^{-1} + a_2 z^{-2} + a_n z^{-n}\right]} \xi_t \qquad 4.27$$

where z denotes the shift operator, or z-transform, and ξ is assumed to be a sequence of uncorrelated Gaussian random variables. This is known as an auto-regressive-moving-average (ARMA) model. It can be shown to be a canonical form for noise which is stationary and possesses a rational spectral density (9). In fact, almost all practically obtained noise sequences can be adequately represented in this manner. The coloured noise in equation 4.27

can be conceptually thought of as having been created by passing white noise through a linear filter. This form of noise model was first used in the engineering system identification field for I/O identification by Astrom and Bohlin (11). However, it has also been extensively used in the statistical analysis of time series where there was no explicit input, noteably by Box and Jenkins (39).

We will now consider the properties of an estimator with the noise modelled in this manner. The difference between this and the OLS estimator is shown in Fig. 4.4. In the following we will consider only the first order noise model for simplicity, although the analysis can be trivially generalised to noise models of any order.

The first order ARMA noise model is

$$e_t = \frac{1 + b\,z^{-1}}{1 + a\,z^{-1}} \xi_t \qquad 4.28$$

this gives the recursive relationship for e_t as

$$e_t = -a\, e_{t-1} + \xi_t + b\,\xi_{t-1} \qquad 4.29$$

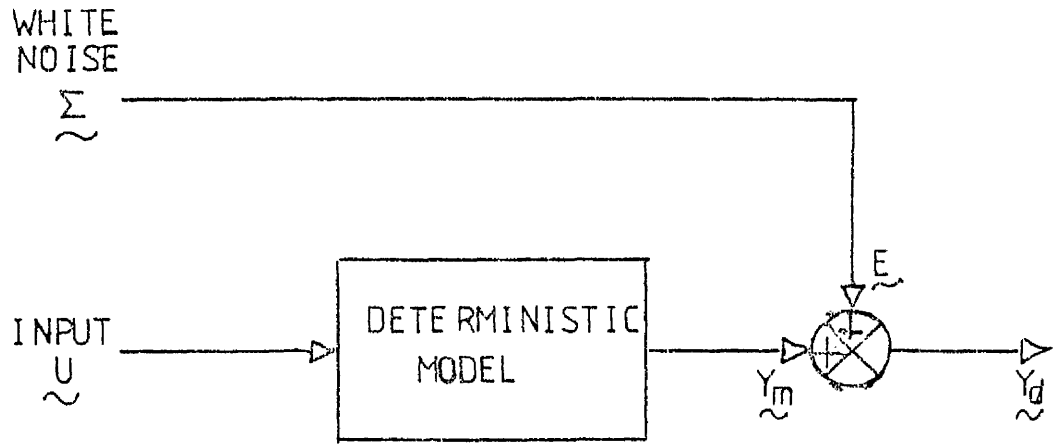
this is easily transformed to get ξ_t if e_t is known.

$$\xi_t = e_t + a\, e_{t-1} - b\,\xi_{t-1} \qquad 4.30$$

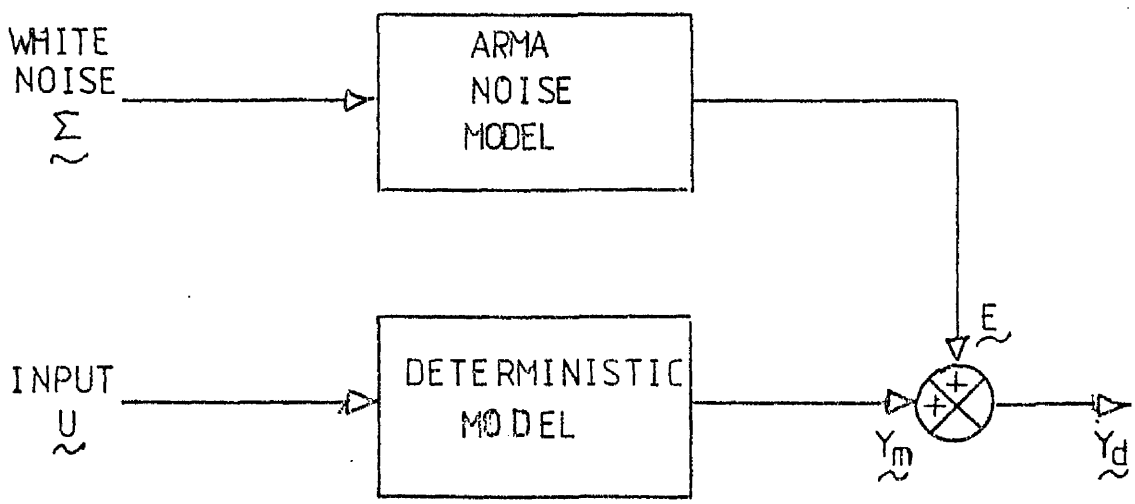
Although equations 4.29 and 4.30 are in a convenient form for recursive computation, for the subsequent analysis it is more convenient to adopt a matrix vector formulation. The dependence of the (m x 1) vector of correlated observations e on the vector of (assumed) white residuals ξ can be written as

$$e = Q\xi \qquad 4.31$$

where Q is the $m \times m$ matrix



LEAST SQUARES MODEL



MAXIMUM LIKELIHOOD MODEL

FIGURE 4·4

$$Q = \begin{bmatrix} 1 & & & & \\ (b-a) & 1 & & & \\ -a(b-a) & (b-a) & 1 & & \\ \vdots & & \ddots & & \\ (-a)^{m-2} & (b-a) & & & 1 \end{bmatrix} \qquad 4.32$$

Note that Q is unit lower triangular. The inverse relationship can be similarly written as

$$\mathcal{E} = Q^{-1} e \qquad 4.33$$

where Q^{-1}, which is also unit lower triangular, can be explicitly written as

$$Q^{-1} = \begin{bmatrix} 1 & & & & \\ (a-b) & 1 & & & \\ -b(a-b) & (a-b) & & & \\ \vdots & & \ddots & & \\ (-b)^{m-2} & (a-b) & & & 1 \end{bmatrix} \qquad 4.34$$

Recall from Section 4.3, Equation 4.19 that if the fitting errors e are assumed Gaussian, although not necessarily independent, their conditional p.d.f. is

$$\text{prob}\,(e / \beta, N(a,b)) = (2\pi)^{-\frac{m}{2}} (\det N)^{-\frac{m}{2}} \exp\left\{ -\tfrac{1}{2} e^T N^{-1} - e \right\} \qquad 4.35$$

The probability has also to be written as conditional on the noise covariance N

in the equation above since this is also being explicitly considered as a parameter (i.e. via a and b) in this situation. The log likelihood function for this becomes

$$\log L (\beta , N) = - \frac{m}{2} \log (2 \pi) - \frac{m}{2} \log (\det N) - \tfrac{1}{2} e^T N^{-1} e \qquad 4.36$$

To obtain the maximum likelihood estimate it is necessary to differentiate the above wrt the noise parameters as well as the deterministic model parameters simultaneously. However, as we shall see, the problem is rendered separable by the choice of the noise model structure. From equation 4.31 and the fact that ξ is assumed to be an uncorrelated random sequence with covariance matrix given by equation 4.17, the covariance matrix of the additive fitting errors becomes

$$N = E\{ e \; e^T \} = E\{ Q\xi \; (Q\xi)^T \} = E\{ Q \xi \xi^T \; Q^T \}$$

$$= Q \; E\{ \xi\xi^T \} \; Q^T = \hat{\sigma}^2 \; Q \; Q^T \qquad 4.37$$

also

$$\det (N) = \sigma^2 \det (Q) \det (Q^T) = \sigma^2 \qquad 4.38$$

since the determinant of a unit lower or upper triangular matrix is unity.

It is easily seen from this that the problem of maximising the likelihood function with respect to the ($n \times 1$) parameter vector β and the noise parameters (a, b) reduces to the following equivalent problem of minimising a sum of squares.

$$\min_{\text{w.r.t.}\ \theta} \; V (\theta) = \sum_{i=1}^{m} \xi_i^2 \quad \text{or} \quad \xi^T \xi \qquad 4.39$$

where we define an augmented ((n + 2) x 1) parameter vector θ (which also

includes the noise parameters by

$$\theta = \begin{bmatrix} \beta \\ a \\ b \end{bmatrix} \qquad 4.40$$

Although equation 4.39 would appear to be analogous to the case of ordinary least squares, this analogy is not total. A closed form solution to equation 4.39, equivalent to equation 4.12, unfortunately does not exist; even in the case of a process model linear in its parameters. This is due to the way the noise parameters enter into the equation. Thus, for this technique the iterative function minimisation techniques described in Chapters 5 and 6 are a necessity.

Following a similar mathematical argument to the ordinary least squares case, an unbiased estimate of σ^2 is

$$\hat{\sigma}^2 = \frac{1}{m - n} \, \varepsilon^T \varepsilon \qquad 4.41$$

The covariance matrix of the estimates for the maximum likelihood estimator can be shown to be

$$\text{cov} \, (\hat{\theta}) = \hat{\sigma}^2 \left[Z^T \; Z \right]^{-1} \qquad 4.42$$

where Z is a modified sensitivity matrix of order $m \times (n+2)$ given by

$$Z = \begin{bmatrix} \frac{\partial \varepsilon_1}{\partial \theta_1} & \cdots & \frac{\partial \varepsilon_1}{\partial \theta_{n+2}} \\ \vdots & & \vdots \\ \frac{\partial \varepsilon_m}{\partial \theta_1} & \cdots & \frac{\partial \varepsilon_m}{\partial \theta_{n+2}} \end{bmatrix} \qquad 4.43$$

Confidence sets for the individual parameters and overall confidence ellipsoids can be constructed from $\text{cov} \, (\hat{\theta})$ in a manner analogous to that used in the ordinary least squares case considered in Section 4.3.

The mechanisation of the maximum likelihood estimator will be discussed in Chapter 6 where it will be shown how the modified sensitivity matrix Z can be calculated with reduced overhead from the process model sensitivity matrix X and the fitting errors e .

4.5 Retrospective Tests on the Adequacy of Fit of Estimated Models

After an experiment has been carried out and a model estimated, it is important to verify the original statistical assumptions implicit in the estimation method used. If these are in error the estimates of the covariance matrix of the parameters, etc. may no longer be valid. In some situations the estimates may be biased.

The properties of the estimators discussed in Sections 4.3 and 4.4 depended crucially on the independence of the appropriate residual sequences, i.e. e in the ordinary least squares case and $\dot{\Sigma}$ in the maximum likelihood case. These sequences should thus be examined closely as any structure or dependence on the input displayed by them may suggest deficiencies in the model, or perhaps the presence of unsuspected feedback, which can be a problem in an identification context, particularly where normal operating records are being used (147).

A useful procedure for testing the independence of the residual sequence is to compute an estimate of its serial autocorrelation, e.g.

$$\hat{\phi}_{\varepsilon\varepsilon}(\tau) = \frac{1}{m-\tau} \sum_{k=1}^{m-\tau} \varepsilon(k)\,\varepsilon(k+\tau) \qquad 4.44$$

for a reasonable number of delays $\tau = 1, 2, 3$, etc. Ideally if the residual sequence is independent, i.e. the residuals are 'white', then it should possess an impulsive autocorrelation function (265, Ch. 5). That is $\hat{\phi}_{\varepsilon\varepsilon}(\tau \neq 0)$

should be zero. In reality, however, equation 4.44 is only an estimate over a finite data length, whereas the true autocorrelation implies convolution over infinite data lengths. Hence, this estimate has an associated variance. In Bendat andPiersol (30), the resultant standard deviation of this is shown to be

$$\sigma\left\{\frac{\hat{\phi}_{ee}(\tau)}{\hat{\phi}_{ee}(0)}\right\} = \frac{1}{(m-\tau)^{\frac{1}{2}}} \quad \frac{m}{m-n} \qquad 4.45$$

Note that for a few lags τ only and a large number of observations ' m ' the above formula for the variance of the normalised autocorrelation function (which is what we compute in practice) reduces to

$$\sigma_{norm}\{\hat{\phi}_{ee}(\tau)\} \approx \frac{1}{m^{\frac{1}{2}}} \quad \text{for } m >> \tau \text{ and } m >> n \qquad 4.46$$

Similarly, cross-correlations between the input and the residuals may be carried out to detect the presence of feedback (35,62).

An alternative method for checking for the independence of the residual sequence is examination of the "number of runs". The number of runs is the number of changes of sign of the residuals plus one (e.g. in the sequence + + - - + - there are four runs). For a sequence of m independent random variables, the expected number of runs should be approximately equal to m/2 . A significance test for the independence of the residual sequence based on the number of runs is given in Draper and Smith (93), Chapter 3. In assessing the adequacy of the fitted model it is also important to check if the fit of the model is significantly improved by adding extra parameters, e.g. in the case of the homogeneous CO_2 gas exchange model by going from 4 to 6 parameters.

The determination of the order of the model can in fact be approached

as a statistical hypothesis testing problem.

To test if the criterion function is significantly reduced when the number of parameters is increased from n_1 to n_2 say, the following test quantity can be used (145)

$$f = \frac{\left[V(\beta_{n1}) - V(\beta_{n2})\right]\left[m - n_2\right]}{\left[V(\beta_{n2})\right]\left[n_2 - n_1\right]} \qquad 4.47$$

If the residuals are Gaussian (or in practice approximately so) this test quantity f can be shown to be approximately F - distributed with $(n_2 - n_1)$ and $(m - n_2)$ degrees of freedom. Thus, for a given significance level α (usually 5%) the increase in model parameters is said to result in a significant improvement if the corresponding test quantity f is such that

$$f > F_{1-\alpha}(n_1 - n_2, m - n_2) \qquad 4.48$$

where $F_{1-\alpha}(n_1 - n_2, m - n_2)$ is found from a table of the F distribution (59).

Akaike (2) has proposed an alternative procedure for model order selection derived on information theoretic grounds. He formulates the model order testing procedure essentially as an estimation problem. This has the advantage that the need for subjective judgement, i.e. in selecting significance levels, such as required for the F - ratio test, is eliminated. However, the method requires that an estimate of the likelihood function be explicitly computable. Akaike advocates choosing the model order such that the following information criterion is minimised.

$$AIC_n = -2 \log L(\hat{\beta}_n) + 2n \qquad 4.49$$

where $L(\hat{\beta}_n)$ is an estimate of the likelihood function based on 'n' independently adjusted parameters. In terms of $V(\hat{\beta}_n)$ (V being given be either equation 4.11 or 4.39), equation 4.49 becomes

$$AIC_n = m \left\{ \log \left(\frac{2\pi}{m} V(\hat{\beta}_n) \right) + 1 \right\} + 2n \qquad 4.50$$

Successful applications of the above criterion have been reported (167, 223, 227). However, claims that the order testing procedure is in fact truely "objective" have been disputed (263).

Another important consideration when assessing adequacy of fit of an estimated model is that of stationarity or time invariance of the parameter estimates. This can be checked by estimating models in turn over the first and second half of the data sequence and ensuring the estimates are not significantly different from those obtained from fitting over the entire data sequence.

4.6 Identifiability Aspects

As discussed in Chapter 1, the emphasis is usually slightly different in identification of biological as opposed to the industrial processes. In industrial process identification the primary aim is to create models which accurately mimic the real systems observed external behaviour. In the biological area, however, in addition to this, the investigator is likely to be concerned as to how the parameters of the derived models relate to physical quantities. In this latter situation, it is obvious that this will only be valid if the model is configured in a manner such that all its internal parameters of interest can be uniquely identified. More mathematically, this requires that the mapping from parameter space to the input/output relation should be injective. Such a model is said to be identifiable.

Bellman and Astrom (28) first explicitly formulated and discussed this problem in the context of biological compartmental systems in 1970. They advocated classical transfer function theory as a suitable mechanism to investigate this. They showed that each coefficient of the resultant transfer function matrix

can be expressed as a non-linear combination of the unknown parameters thus defining a set of non-linear equations. Provided these have a unique solution, they state the model is identifiable.

Applications of this s-domain approach to the identifiability of models of drug kinetics have been reported by Milanese and Molino (208,211).

More general identifiability results have been attempted by Cobelli and Romanin-Jacur (69,70,71) based on the analysis of the compartmental diagram (i.e. the signal flow) and hence attempting to avoid explicit calculation of the transfer function matrix (and the matrix conversion problems inherent in this procedure). However, these results have aroused considerably controversy in the literature (81,82, 87, 67, 307). This is concerned with whether the results of Cobelli and Romanin-Jacur form sufficient or even necessary conditions for identifiability, (81, 82), and also with the nature of the relationship of identifiability to the properties of controllability and observability (95) put forward by these authors.

More recently, Cobelli et al (68) have revised their results and have shown conclusively the properties of input and output connectability (78) to be necessary conditions for identifiability. However, in the general case at least, no sufficient conditions have as yet been put forward in the literature.

An algebraic identifiability criterion has been proposed by Grewal and Glover (141). This is based on the evaluation of the rank of the jacobian of the Markov parameter matrix defined as :

$$H(\beta) \quad \begin{bmatrix} C(\beta) & B(\beta) & \\ C(\beta) & A(\beta) & B(\beta) \\ C(\beta) & A^{2n-1}(\beta) & B(\beta) \end{bmatrix} \qquad 4.51$$

where β is the parameter vector of dimension 'n' and A, B, C are the usual

matrices obtained by configuring the system in state space form (95). In the biomedical field this technique has been applied to models of thyroid hormone metabolism (88, 89).

So far when discussing identifiability we have really been inferring what Bellman and Astrom (28) call global structural identifiability. This depends only on the structure of the model and available input/output ports and not on the numerical values of the parameters. However, this is only really one aspect of the problem and as noted by Brown and Godfrey (49) there exists far wider implications. That is, certain situations may arise where although the model may be theoretically identifiable in the sense discussed above, practically due to e.g. poor experimental design, or inaccurate measurements, one may be unable to resolve these parameters uniquely. Brown and Godfrey (49) coin the term 'determinacy' to refer to this near or pathological type of identifiability.

One example of this is the following simple algebraic model

$$Y_M = \beta_1 + \beta_2 (10 + u) \qquad 4.52$$

For this model, in the presence of noise, both parameters can only be (easily) uniquely estimated for large values of the input u. For $| u |$ small only $\beta = \beta_1 + 10 \beta_2$ can be estimated uniquely. Many other cases similar to this can be cited. These may not be at all obvious, especially in the dynamic case where it may not be possible to manipulate the model equations so that groups of parameters appear together allowing potential unidentifiability to be deduced. The existence of some sort of criteria that could be applied to detect this retrospectively would obviously be a convenient tool in this situation. In fact, it transpires such criteria can be derived from consideration of the appropriate sensitivity matrices (X for OLS and Z for ML), discussed earlier in this

chapter.

Beck and Arnold (22) show that the parameters can be estimated if the sensitivity coefficients over the range of observations are not linearly dependent. That is,e.g. in the ordinary least squares case, the matrix $\frac{1}{\sigma^2} X^T X$ (which is proportional to the inverse of the parameter covariance matrix C if the residuals are white) is not rank deficient. In simple cases this unidentifiability may be deduced from examination of time plots of the sensitivities. However, it is difficult to detect complicated interdependencies in this manner. If an eigenvalue/eigenvector decomposition of C indicates the eigenvalues are of greatly differing magnitudes, this suggests identifiability problems. A very useful check on the correlations between particular pairs of parameters is to compute the parameter correlation matrix R defined as (220):

$$r_{ij} = \frac{C_{ij}}{(C_{ii} C_{jj})^{\frac{1}{2}}} \qquad 4.53$$

where C_{ij}, C_{ii}, C_{jj}, etc. are elements of the parameter covariance matrix. Note that the diagonal terms of the correlation matrix R will be unity and the off diagonal terms such that

$$-1 \leq r_{ij} \leq 1 \qquad 4.54$$

Near unidentifiability is indicated by the modulus of one or more of the off-diagonal terms of R being near unity, i.e. the parameters in question are highly correlated. In practice, estimates for parameters i and j are suspect if (22)

$$| r_{ij} | > 0.95 \qquad 4.55$$

Small off-diagonal elements of the R matrix indicate that the parameters are essentially decoupled.

4.7 Structural Identifiability of the Homogeneous CO_2 Model

The structural identifiability of the model may be approximately investigated by considering the constant ventilation version of the model.

$$S\dot{V} = \dot{V} \text{ effective} = \text{const.} \qquad 4.56$$

where the value of $\dot{V}$ effective is taken from the Bohr equation (Chapter 2, Section 2.5),

$$\text{i.e. } \dot{V} \text{ effective} = (\dot{V}_I - f\dot{V}_D) \qquad 4.57$$

By taking Laplace transforms of the model equations 2.43 and 2.44 and after some manipulation, the model can be expressed in the following form :

$$P_A(S) = \frac{\alpha_1 S + \alpha_2}{S^2 + \alpha_3 S + \alpha_4} \cdot P_I(S) + \frac{\alpha_5 S + \alpha_6}{S^2 + \alpha_3 S + \alpha_4} + \frac{\alpha_2}{S} \qquad 4.58$$

where $P_A(S)$ is the Laplace transform of the 'output', i.e. alveolar PCO_2 and $P_I(S)$ is the Laplace transform of the 'input' viewed as inspired PCO_2. The set of Laplace transform coefficients α_k are functions of the parameters β and are given by

$$\alpha_1 = \frac{\dot{V}\,\text{eff}}{V_A} \qquad 4.59$$

$$\alpha_2 = \frac{\dot{Q}\dot{V}\,\text{eff}}{V_A V_{TC}} \qquad 4.60$$

$$\alpha_3 = \frac{\dot{Q}}{V_T} + \frac{\dot{V}\,\text{eff}}{V_A} + \frac{\text{const}\,\dot{Q}b}{V_A} \qquad 4.61$$

$$\alpha_4 = \frac{\dot{Q}\dot{V}\,\text{eff}}{V_A V_{TC}} \qquad 4.62$$

$$\alpha_5 = P_{A(0)} - \text{const}\,\frac{\dot{M}}{\dot{V}\,\text{eff}} \qquad 4.63$$

$$\alpha_6 = \frac{\dot{Q}}{V_{T_C}} P_{A(0)} + \frac{\dot{Q}\,A_{INT} \times \text{const}}{V_A} + \frac{\text{const}\,\dot{Q}b}{V_A} P_{T_C(0)} - \text{const}\,\frac{\dot{M}}{\dot{V}\,\text{eff}} \frac{\dot{Q}}{V_{T_C}} + \frac{\dot{V}\,\text{eff}}{V_A} + \frac{\text{const}\,\dot{Q}b}{V_A} \qquad 4.64$$

$$\alpha_7 = \frac{\text{const } \dot{M}}{\dot{V}\text{eff}} \qquad 4.65$$

The first term on the right-hand side of equation 4.58 is the dynamic term due to the input and the second term is the initial condition response. This term is non-existent if the model is initially in a steady state. The third term is an offset term. This latter term is expected due to the fact that there is non-zero output for zero input (i.e. under normal air breathing conditions $P_A CO_2$ = 40 mm Hg for $P_I CO_2$ = 0 mm Hg).

The dominant poles of the system are given by the roots of the equation

$$S^2 + \alpha_3 S + \alpha_4 = 0 \qquad 4.66$$

For reasonable parameter values ($\dot{Q}$ = 5 L/M , V_A = 5L , $\dot{M}$ = 0.2 L, V_{T_C} = 5 L) this gives two left half plane poles, i.e.

$$S_1 = -5.8 , \quad S_2 = -0.2 \qquad 4.67.$$

This corresponds to time constants of approximately 10 secs and 5 mins respectively. The first time constant represents the relatively fast dynamics of the alveolar compartment, while the second represents the relatively slower tissue compartment dynamics.

We will now consider the global identifiability aspects of this model structure, i.e. assuming a 'good' (informative) experiment, how many parameters can be uniquely estimated ?

It is not easy to tackle this problem via the more formal Grewal and Glover (141) approach because of difficulty in representing the model in standard linear time invariant, state space form. This is entirely due to the manner in which $\dot{M}$ enters into the model equations. Therefore, if we think of this as an input we can write the model equations in standard form. We explicitly consider, however, $\dot{M}$ as a parameter. We, therefore, adopt

the following more intuitive approach to the identifiability analysis.

In principle, all the independent Laplace transform coefficients α_k in the Laplace transform representation of the model (equation 4.58) are determinable from input/output experiments. Thus, the number of these coefficients implicitly defines an upper bound on the maximum number of intrinsic model parameters which might be identifiable (68).

Coefficients α_2 and α_4 essentially contain the same information since one is a multiple of the other. Expressing the remaining transform coefficients in terms of the intrinsic model parameters results in the following equations

$$V_A = k_1 \qquad 4.68$$

$$\dot{M} = k_2 \qquad 4.69$$

$$P_{A(0)} = k_3 \qquad 4.70$$

$$b\dot{Q} = k_4 \qquad 4.71$$

$$b\,V_{T_C} = k_5 \qquad 4.72$$

$$P_{T_C(0)} + \frac{A_{INT}}{b} = k_6 \qquad 4.73$$

Examination of the above equations show why attempts to estimate b, the slope of the CO_2 dissociation curve and/or A_{INT} the intercept of the dissociation curve, met with failure in the previous chapter. Note how a change in b in equations 4.60 - 4.64 can be exactly compensated for by a change in $\dot{Q}$, V_{T_C} and $P_{T_C(0)}$, thus giving the same set of Laplace transform coefficients and, therefore, the same model response. Also, a change in A_{INT} can be compensated for exactly by a change in $P_{T_C(0)}$ in equation 4.64 thus again yielding the same model output. Equations 4.68 - 4.73 tell us, however, that if b and A_{INT} are known, then the model parameterisation in terms of $\dot{Q}$, V_A, $\dot{M}$, V_{T_C}, $P_{A(0)}$ is unique.

It must be emphasised that the above results yield only minimal necessary conditions for obtaining unique estimates, i.e. under ideal experimental conditions. It gives us no information on the degree of identifiability. As discussed in Section 4.6, this can only be inferred retrospectively.

4.8 Validation Data : Estimation Results for 4, 6 and 8 Parameter Models

The parameter estimates obtained by fitting four parameter models (i.e. assuming steady-state initial conditions) to the validation data were given in the previous chapter and the physiological significance of these discussed. In this section we will assess the adequacy of these fitted models and compare them with the results obtained by fitting a six parameter model (i.e. estimating additionally the initial conditions $P_{A(0)}$ and $P_{Tc(0)}$) and an eight parameter model (includes 2 additional noise parameters for the first order ARMA model).

The estimation results for the 4,6 and 8 parameter models are detailed in Appendix A, together with their respective variances as calculated using the appropriate formulae derived earlier in this chapter.

Originally these estimates were computed using the Factorised-Quasi-Newton Methods discussed in Chapter 5. These techniques do not explicitly utilise sensitivity information. When using these techniques, it was therefore necessary to write a separate programme to compute the sensitivity matrix by finite differences to allow the parameter estimate variances to be calculated. Later, however, sums of squares were used which yielded the sensitivity matrices as part of the function minimisation process thus allowing the parameter estimates variances to be calculated directly. (Generally the fits are very good, i.e. M.S.E $<$ 1% of the mean output value.)

These results serve to indicate that the assumption of steady state initial conditions (i.e. four parameter model) is not in fact correct in every

data file as assumed in previous work in this project (228, 234). Very frequently a six and even eight parameter model gives far smaller values of the criterion function $V(\beta)$. However, there does not seem to be any 'best' structure to assume in the global sense (i.e. over all the validation data) since on some files increasing the model order did not seem to make a great deal of difference.

No one model order gives the best agreement with the dye dilution estimates either since the fourth order model gives the nearest value 22/50 times, the sixth order model 16/50 times and the eight order model 13/35 times. On a more formal level, the question of the most appropriate model order was investigated using the structure testing techniques of Section 4.5.

The test quantity defined by equation 4.47 was formed for the increase in the number of parameters from four to six and from six to eight. This was then compared with the appropriate value from the F distribution to test if the order increase was significant at the 5% level. These results are given in Table 4.1. These again confirm that different model orders would appear to be appropriate on different data sets. In testing the increase in order from four to six parameters 26/48 times the test indicated the increase in order was significant (22/48 times not significant). As regards the increase in order from 6 to 8 parameters, this was significant 15/34 times. On four occasions the test indicated the increase in order $4 \rightarrow 6$ was not significant, but $6 \rightarrow 8$ was. In this situation the eighth order model was chosen since the test of increase in order from $4 \rightarrow 8$ was computed and found to be significant. Overall, the frequency of chosen model orders are summarised below.

51 data sets compared

n = 4	-	17 data sets
n = 6	-	18 data sets
n = 8	-	16 data sets.

Table 4.1 F-RATIO TEST RESULTS TO CHOOSE 'BEST' MODEL

File	N	$\Sigma e_{i_4}^2$	$\Sigma e_{i_6}^2$	$\Sigma e_{i_8}^2$	f(4→6)	f(6→8)	F(4→6)	F(6→8)	Chosen Order
VALO41	64	1.766	1.634	1.598	2.343	0.631	3.15	3.15	4
2	46	4.666	4.570	4.273	0.420	1.321	3.23	3.23	4
3	45	3.816	2.658	1.899	9.495	7.394	3.23	3.23	8
4	40	3.538	2.399	C	8.071	-	3.32	-	6
VALO51	22	1.759	1.176	1.126	3.966	0.311	3.63	3.74	6
2	20	2.868	1.088	C	11.452	-	3.74	3.89	6
3	24	1.208	0.838	0.721	3.973	1.298	3.55	3.63	6
VALO72	28	1.671	1.599	1.124	0.495	4.226	3.44	3.49	8
3	28	C	C	C	-	-	-	-	-
4	25	1.931	1.738	1.667	1.055	0.362	3.55	3.63	4
VALO81	27	2.560	1.188	1.070	12.126	1.048	3.44	3.49	6
4	20	1.488	0.949	C	3.975	-	3.74	-	6
5	22	1.553	1.080	FM	3.503	-	3.63	-	4
VAL101	31	2.855	1.549	0.997	10.539	6.367	3.34	3.40	8
2	30	2.728	1.689	1.576	7.382	0.789	3.40	3.44	6
3	31	3.400	2.992	C	1.704	-	3.34	-	4
4	28	6.871	6.172	5.207	1.245	1.853	3.44	3.49	4
VAL111	42	4.400	4.164	4.027	1.020	0.578	3.28	3.30	4
2	37	8.646	4.519	3.258	14.155	5.162	3.30	3.32	8
3	36	6.456	2.592	1.404	22.361	5.419	3.34	3.37	8
4	37	6.355	2.325	1.727	26.867	5.020	3.30	3.32	8
VAL122	41	6.114	5.440	4.990	1.920	1.487	3.32	3.32	4
3	37	C	3.878	2.591	-	7.202	-	3.32	8
4	36	13.741	7.848	C	11.263	-	-	-	6
5	45	7.384	6.770	2.810	1.768	26.071	3.23	3.23	8
VAL141	30	2.939	2.414	2.154	2.609	1.327	3.40	3.44	4
2	27	1.767	1.296	1.071	3.816	1.996	3.44	3.49	6
3	30	C	2.966	2.359	-	2.830	3.40	3.44	6
4	29	3.153	2.473	2.042	3.162	2.216	3.40	3.44	4
VAL161	21	8.423	3.040	C	13.280	-	3.63	-	6
2	22	2.849	1.332	FM	9.111	-	3.63	-	6
3	21	6.800	6.446	FM	0.412	-	3.63	-	4
4	21	2.818	2.225	FM	1.998	-	3.63	-	4

cont'd.....

Table 4.1 (cont'd.....)

File	N	$\Sigma e_{i_4}^2$	$\Sigma e_{i_6}^2$	$\Sigma e_{i_8}^2$	f(4→6)	f(6→8)	F(4→6)	F(6→8)	Chosen order
VAL 172	37	6.553	3.635	2.167	12.443	9.823	3.30	3.32	8
3	39	9.046	6.753	3.755	5.602	12.375	3.30	3.32	8
4	38	3.780	3.741	2.512	0.167	7.339	3.30	3.32	8
VAL 181	22	1.700	0.658	FM	12.668	-	3.63	-	6
3	24	3.346	1.392	FM	12.634	-	3.55	-	6
4	29	3.059	2.657	2.656	1.759	0.004	3.40	3.43	4
VAL 191	23	2.465	2.035	1.674	1.796	1.617	3.55	3.63	4
VAL 203	38	4.816	4.325	FM	1.816	-	3.32	-	4
VAL 221	49	4.709	4.105	1.287	3.163	44.886	3.23	3.23	8
2	50	3.667	3.479	2.286	1.189	10.959	3.23	3.23	8
3	53	7.477	4.420	3.228	16.253	8.308	3.23	3.23	8
4	51	3.781	2.925	1.532	6.584	19.549	3.23	3.23	8
VAL 231	31	5.877	3.957	3.515	6.065	1.446	3.34	3.40	6
2	22	1.241	1.109	FM	0.952	-	3.63	-	4
3	25	2.715	1.924	FM	3.905	-	3.55	-	6
VAL 251	29	3.064	1.937	C	5.527	-	3.40	-	6
2	28	1.920	1.649	1.303	1.807	2.655	3.44	3.49	4
3	30	2.346	1.483	1.382	6.983	0.803	3.40	3.44	6
4	31	C	C	2.983	-	-	-	-	8

C denotes programme crash.
FM denotesfalse minimum located.

One feature of the results of Table 4.1 is that the criterion for model order is statistically not very "sharp", i.e. very powerful. Because the value of the test quantity is so low, the results of the tests depend greatly on the value of significance level, i.e. some results would be different at smaller 'subjective' significance levels. The 'best' model orders were also assessed using Akaike's 'objective' method (see Section 4.7). The results are given in Table 4.2 where the AIC (Akaike Information Criterion) is computed for each model order using equation 4.50. Using Akaike's method predicts identical results to the F- test 39 out of 51 occasions. On the data files where the two methods disagree (invariably this is where the F-test statistic is fairly close to test value), Akaike's method in this situation is seen to consistently predict a higher order model. This was also noticeable with results reported by Astrom and Kallstrom (14) in identifying models of ship-steering dynamics.

It would also be interesting to assess how often the 'best' order as chosen by the F-test corresponds to that model order (4, 6 or 8) which gives a value of cardiac output, which is nearest the dye-dilution value. In fact, these correspond on only 17 data sets, which unfortunately is not any better for the results for any particular model order given above.

It is difficult to assess if this is significant, however, since we are comparing two quantities, both of which may have significant variances associated with them. A direct plot of the cardiac output estimates for the 'best' model against the dye values is given in Figure 4.5. This shows 36/48 pairs of estimates within $\pm$ 20%, which compares similarly with 37/51 for the four parameter model (see Chapter 3). Table 4.3 gives a statistical summary of these comparisons.

Before going on to consider the implications of the estimated parameter

Table 4.2 AKAIKES INFORMATION CRITERION RESULTS TO CHOOSE 'BEST' MODEL ORDER

File	N	$\sum e_{i_4}^2$	$\sum e_{i_6}^2$	$\sum e_{i_8}^2$	AIC_4	AIC_6	AIC_8	Chosen order
VALO41	64	1.766	1.634	1.598	-40.18	-41.15	-38.58	6
2	46	4.666	4.570	4.273	33.26	36.30	37.20	4
3	45	3.816	2.658	1.899	24.646	12.37	1.241	8
4	40	3.538	2.399	C	24.48	1.294	-	6
VALO51	22	1.759	1.176	1.126	14.84	9.99	13.03	6
2	20	2.868	1.088	C	25.91	10.52	-	6
3	24	1.208	0.838	0.721	4.36	-0.418	-0.027	6
VALO72	28	1.671	1.599	1.124	8.52	11.29	5.417	8
3	28	C	C	C	-	-	-	-
4	25	1.931	1.738	1.667	14.913	16.28	19.24	4
VALO81	27	2.560	1.188	1.070	21.00	4.27	5.45	6
4	20	1.488	0.949	C	12.78	7.79	-	6
5	22	1.552	1.080	FM	12.10	8.112	-	6
VAL101	31	2.855	1.549	0.997	22.02	7.07	- 2.59	8
2	30	2.728	1.689	1.576	21.19	10.81	12.73	6
3	31	3.400	2.992	C	27.44	27.48	-	4
4	28	6.871	6.172	5.207	48.11	49.10	48.34	4
VAL111	42	4.400	4.164	4.027	32.41	34.09	36.69	4
2	37	8.646	4.519	3.258	59.19	39.19	31.08	8
3	36	6.456	2.592	1.404	48.28	19.43	1.35	8
4	37	6.355	2.325	1.727	47.80	14.59	7.60	8
VAL122	41	6.114	5.440	4.990	46.31	45.52	45.98	6
3	37	C	3.878	2.591	-	33.53	22.60	8
4	36	13.741	7.848	C	75.47	59.31	-	6
5	45	7.384	6.770	2.810	54.35	54.44	18.86	8
VAL141	30	2.939	2.414	2.154	23.43	21.52	22.10	6
2	27	1.767	1.296	1.071	10.99	6.62	5.47	8
3	30	C	2.966	2.359	-	27.70	24.83	8
4	29	3.153	2.473	2.042	25.93	22.89	21.34	8
VAL 161	21	8.423	3.040	C	48.80	31.00	-	6
2	22	2.849	1.332	FM	25.45	12.73	-	6
3	21	6.800	6.446	FM	43.90	46.78	-	4
4	21	2.818	2.225	FM	25.41	24.44	-	6
VAL 172	37	6.553	3.635	2.167	48.93	31.13	15.99	8
3	39	9.046	6.753	3.755	61.67	54.16	35.38	8
4	38	3.780	3.741	2.512	28.12	31.73	20.59	8

cont'd.....

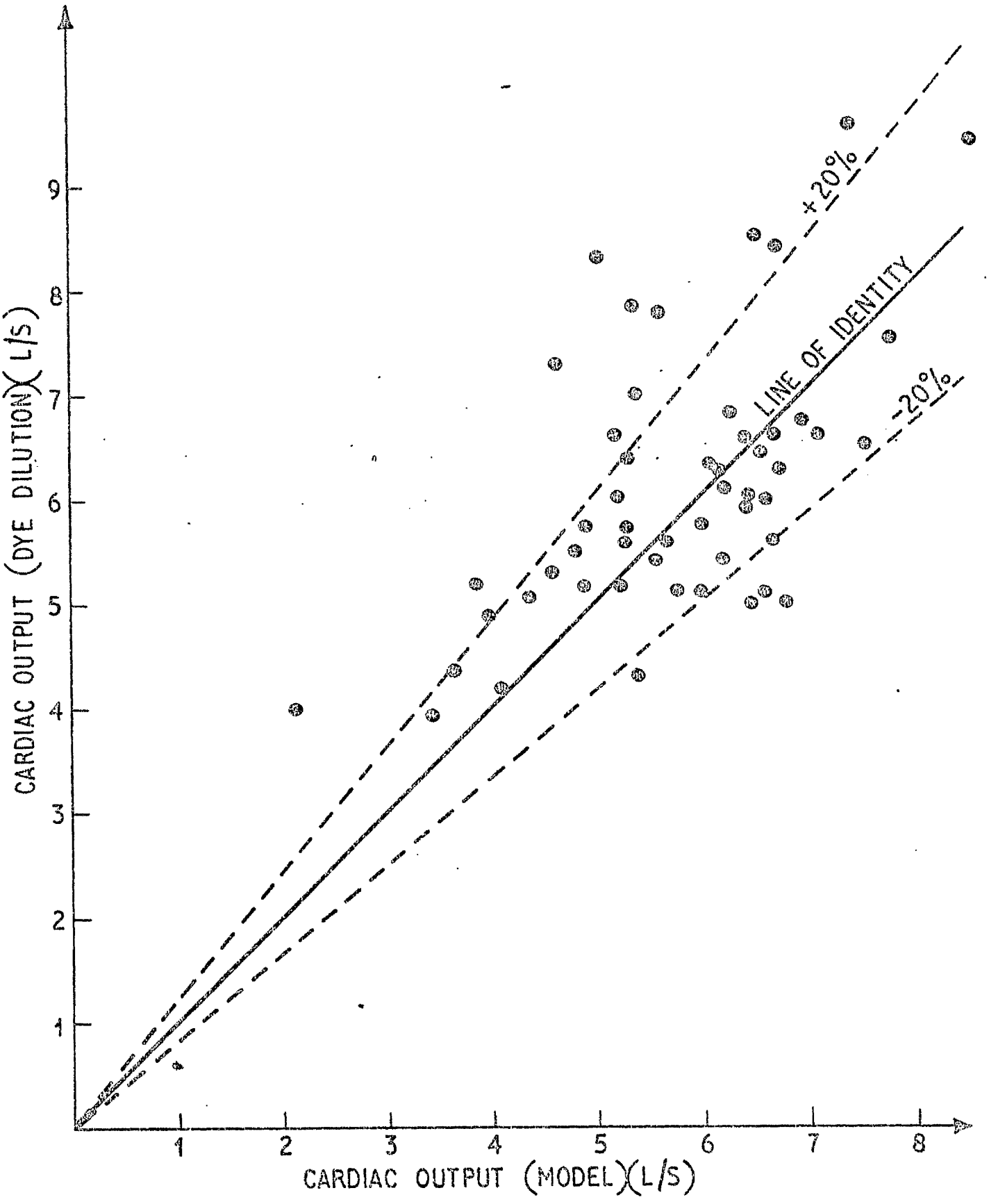
Table 4.2 cont'd.....

File	N	$\Sigma e_{i_4}^2$	$\Sigma e_{i_6}^2$	$\Sigma e_{i_8}^2$	AIC_4	AIC_6	AIC_8	Chosen order
VAL181	22	1.700	0.658	FM	14.09	-2.79	-	6
3	24	3.346	1.392	FM	28.81	11.76	-	6
4	29	3.059	2.657	2.656	25.06	24.97	28.96	6
VAL191	23	2.465	2.035	1.674	21.89	21.48	20.99	8
VAL203	38	4.816	4.325	FM	37.33	37.24	-	6
VAL221	49	4.709	4.105	1.287	32.26	29.53	-23.3	8
2	50	3.667	3.479	2.286	19.24	20.60	3.61	8
3	53	7.477	4.420	3.288	54.58	30.72	18.06	8
4	51	3.781	2.925	1.532	20.01	10.92	-18.00	8
VAL231	31	5.877	3.957	3.515	44.41	36.14	36.47	6
2	22	1.241	1.109	FM	7.17	8.70	-	4
3	25	2.715	1.924	FM	23.43	18.82	-	6
VAL251	29	3.064	1.937	C	25.10	15.80	-	6
2	28	1.920	1.649	1.303	12.41	12.41	9.56	8
3	30	2.346	1.483	1.382	16.67	16.67	8.79	6
4	31	C	C	2.983	-	-	31.39	8

C denotes programme crash

FM denotes false minimum.

RESULTS FOR 'BEST' MODEL USING F-RATIO TEST



VALIDATION DATA

FIGURE 4·5

Table 4.3 : Statistical Summary of Comparative Measurements of Cardiac Output Using 'Best' Model Results as Obtained From F-ratio Test

Files	Corr. Coeff.	Reg. Coeff.	Intercept	Mean Diff. (comp-dye) L/M	S.D. Diff. (comp-dye) L/M	P *
All(51)	0.62	0.64	0.74	-0.15	1.11	NS
7% CO_2(29)	0.81	0.84	1.08	0.10	0.94	NS

* P values obtained from paired Student's t-test (two - tailed),

37/51 paired observations within $\pm$ 20% of line of identity.

Mean reproducibility (dye) - 6.8%

Mean reproducibility (all comp) - 12.2%.

variances, the a priori assumption of residuals being representative of white noise must be checked. This is necessary to ensure that the use of formulae derived earlier in this chapter, to calculate the parameter estimate variances are approximately valid. As noted in Section 4.7, to test the residuals for whiteness in practice one can only test if their (sample) auto-covariance is zero for a number of lags. That is, check the number of points outside the 2σ (95% confidence) limits. Alternatively, the runs test (93) may be used. For the 'best' model order as chosen by the F-ratio, these results are summarised in Table 4.4. Note that in 28/49 cases the residuals for the 'best' model are in fact uncorrelated according to both tests as compared to 13/49 cases correlated. Only in eight instances do the two sets conflict. Thus, these results indicate that the assumption of white residuals is satisfied in the majority of cases.

In fact, the auto-correlation functions of the residuals with increasing model order can themselves be used to give an indicate of correct model order since the residuals sequence will be correlated if the model order is chosen too small (145).

Consider the fits for n = 4, 6, 8 for the files VAL041.PRO and VAL221.PRO. The F-ratio test indicated a four parameter model to be appropriate to fit data file VAL041, whilst an eight parameter model was appropriate for file VAL221. The three sets of residual autocorrelations for n = 4, 6 and 8 are plotted in Figure 4.6 for file VAL041 and Figure 4.7 for file VAL221. Note that for file VAL041, where a four parameter model was sufficient, the A.C.F's. for n = 4, 6, 8 are 'experimentally white' (i.e. no points outside the 95% confidence limits). This is to be compared with the results for file VAL221 where, since an eight parameter model is appropriate, we have 'non-experimentally white' auto-correlation functions for n = 4 and n = 6. Runs test results are (t = 1.96).

Table 4.4 : Tests on Independence of Residuals for Chosen 'Best' Model by F-Ratio Test.

File	Chosen Order	No. of Runs Test value	No. of Points Outside 2$\hat{\sigma}$ limit (10 lags)	Correlated
VALO41	4	0.639	0	N,N
2	4	-3.404	1	Y,Y
3	8	0.111	0	N,N
4	6	-0.097	0	N,N
VAL051	6	-1.966	2	Y,Y
2	6	N.D[1]	-	-
3	6	-1.461	0	N,N
VAL072	8	-0.963	0	N,N
3	-			-
4	4	N.D.	2	Y
VAL081	6	-0.729	0	N,N
4	6	N.D.	0	N
5	4	N.D.	1	Y
VAL101	8	0.422	0	N,N
2	6	-0.908	0	N,N
3	4	-1.091	0	N,N
4	4	N.D.	0	N
VAL111	4	-1.674	1	N,Y
2	8	-2.264	0	Y,N
3	8	0.247	0	N,N
4	8	-0.295	0	N,N
VAL122	4	-2.740	0	Y,N
3	8	0.377	0	N,N
4	6	-4.137	2	Y,Y
5	8	-0.450	0	N,N
VAL141	4	-3.450	2	Y,Y
2	6	-1.172	0	N,N
3	6	-3.159	1	Y,Y
4	4	-2.644	1	Y,Y
VAL161	6	N.D.	-	-
2	6	N.D.	0	N
3	4	N.D.	1	Y
4	4	N.D.	1	Y
VAL172	8	0.672	0	N,N
3	8	1.344	0	N,N
4	8	-1.480	1	N,Y

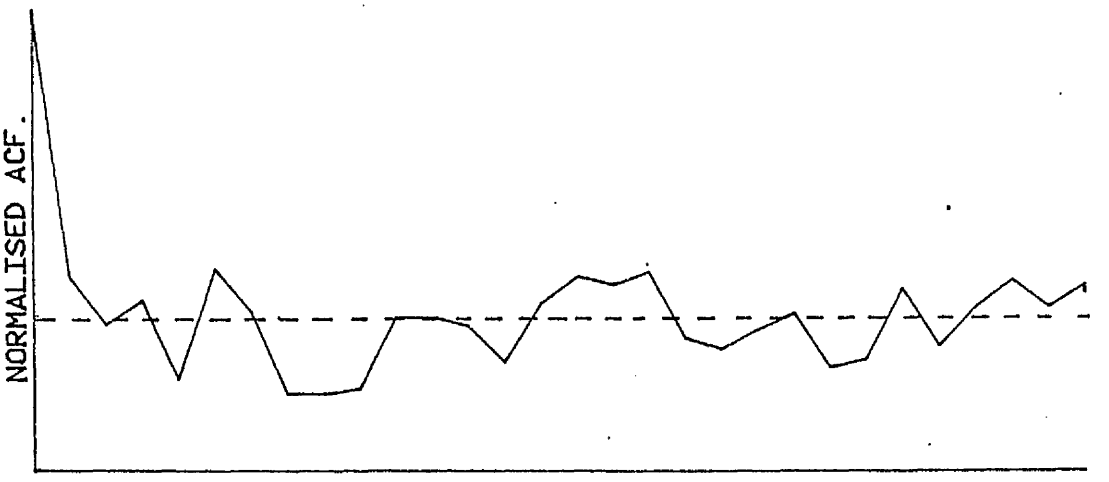
cont'd.....

Table 4.4. cont'd.....

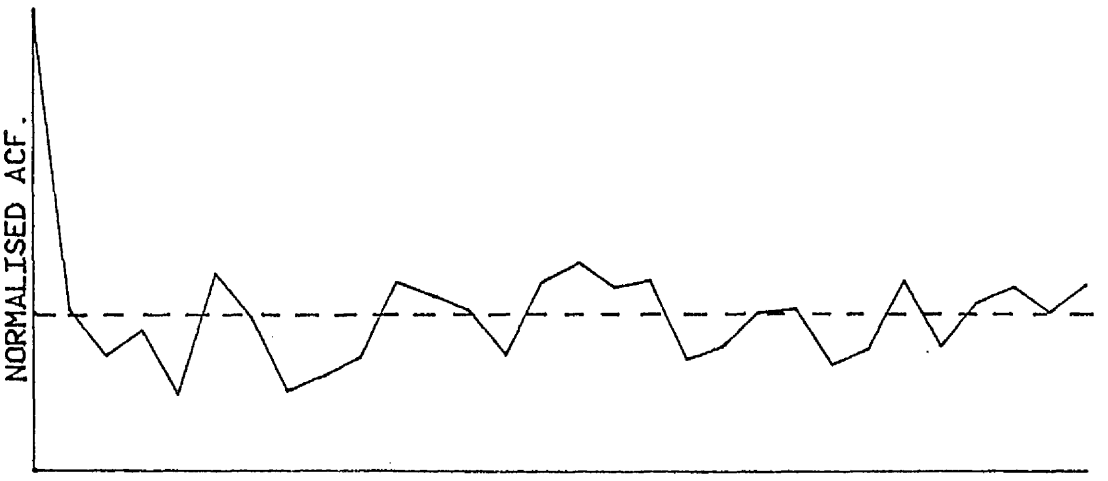
File	Chosen Order	No. of Runs Test value	No. of Points Outside 2$\hat{\sigma}$ Limit (10 Lags)	Correlated
VAL181	6	N.D.	0	N
3	6	1.507	0	N
4	4	-0.372	2	N
VAL191	4	0.009	0	N
VAL203	4	-2.457	0	Y
VAL221	8	1.144	0	N
2	8	-1.277	1	N
3	8	-0.925	0	N
4	8	-0.216	0	N
VAL231	6	-2.554	1	Y
2	4	N.D.	0	N
3	6	-1.585	0	N
VAL251	6	-1.783	2	N
2	4	-2.489	1	Y
3	6	-2.360	1	Y
4	8	-0.684	0	N

Note : N.D. denotes test not defined (to few data points)

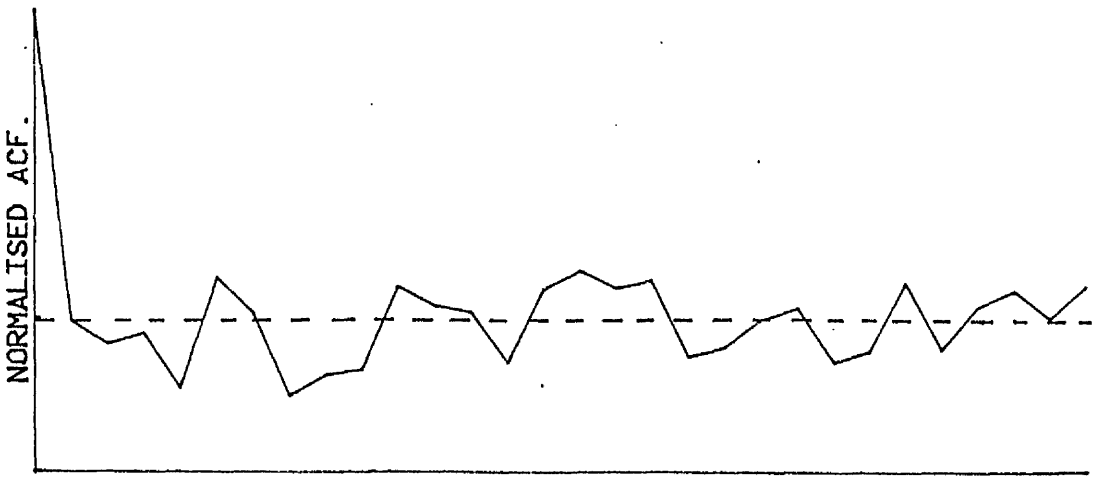
ACF OF RESIDUALS FOR FIT TO FILE VAL041.PRO.



FOUR PARAMETER MODEL.



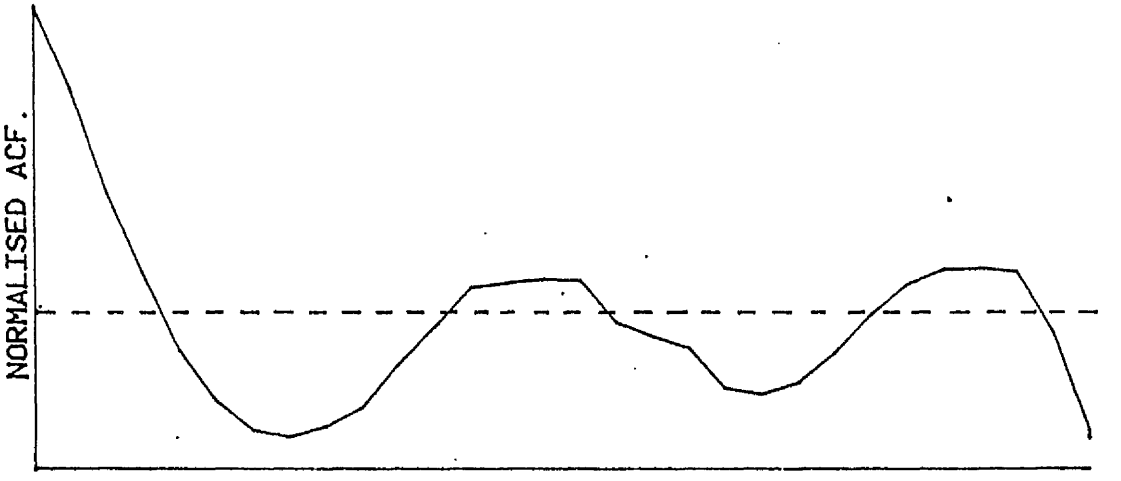
SIX PARAMETER MODEL.



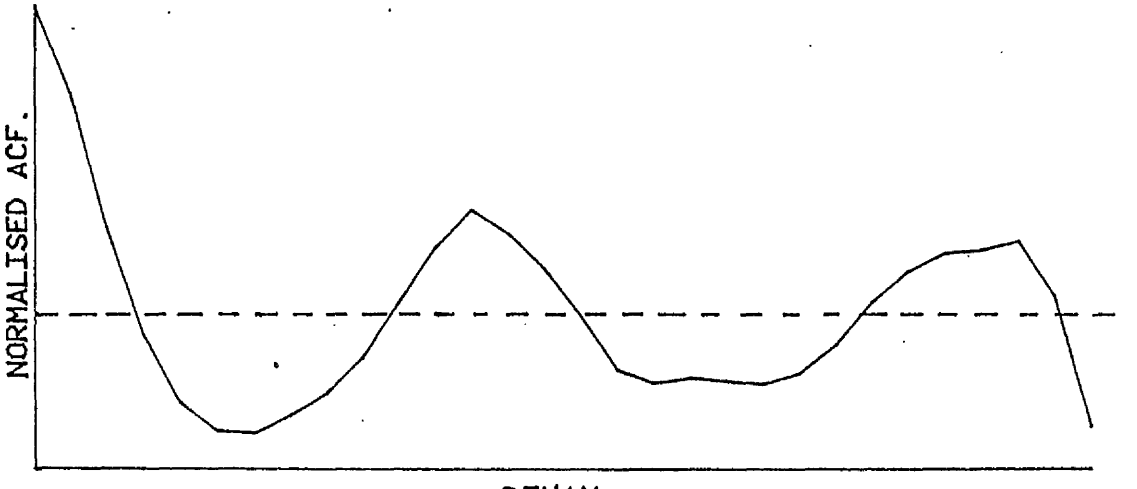
EIGHT PARAMETER MODEL.

FIGURE 4·6

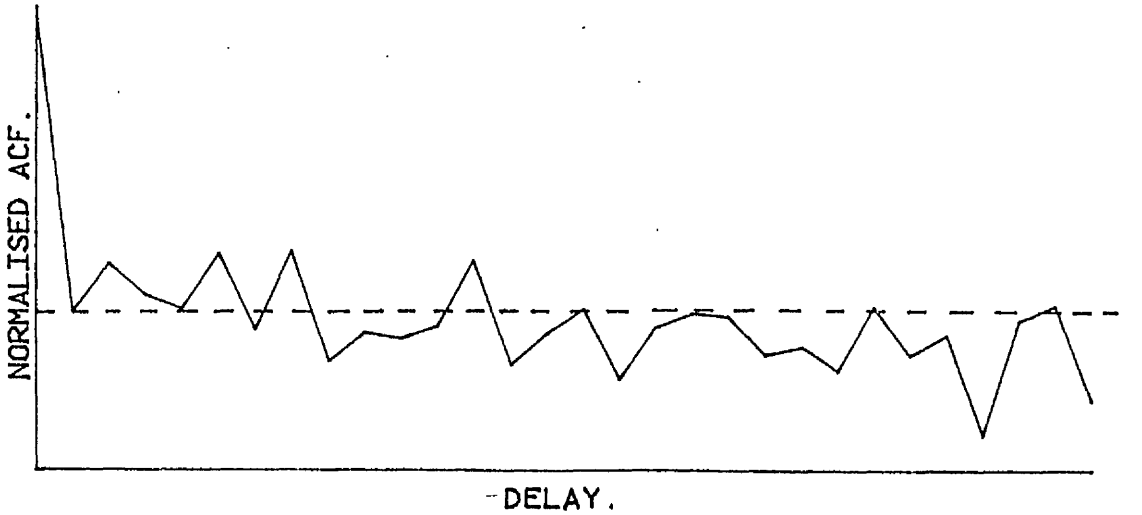
ACF OF RESIDUALS FOR FIT TO FILE VAL221.PRO.



FOUR PARAMETER MODEL.



SIX PARAMETER MODEL.



EIGHT PARAMETER MODEL.

FIGURE 4.7

	n = 4	n = 6	n = 8
VAL041	0.638^{NS}	0.134^{NS}	0.134^{NS}
VAL221	-5.374^{S}	-4.837^{S}	1.114^{NS}

which reinforces this.

A final point to be made about white residuals is as follows. For the eight parameter model, in only about 3 out of the 51 data files were the residuals correlated using the above tests. This tends to confirm the assumption of the sufficiency of the first order ARMA model to represent the errors in these validation experiments.

We will now discuss the degree of identifiability of the estimated models. A number of points become evident from a study of these results :

(1) In only about half of the data files are the dye-dilution estimates within the 95% confidence limits of the 'best' computed $\dot{Q}$ estimates.

(2) Occasionally large variances occur with the estimates of $\dot{M}$ and V_{T_C} in the six and eight parameter model case. e.g. VAL084, VAL163, VAL231. This would tend to suggest local unidentifiability along these parameter directions for these files. To investigate this the sensitivity coefficients for the four and six parameter models were plotted for one of these files (VAL084) and another file for which a six parameter model was appropriate (VAL141), but in which local unidentifiability was not suspected. These are illustrated in Figures 4.8 to 4.11. It is obvious from Figure 4.9 that the sensitivity coefficients for $\dot{M}$ and V_{T_C} for file VAL084 in the six parameter case appear very near to being linearly dependent. As mentioned in Section 4.6 this is a condition for unidentifiability. To check this further the parameter correlation matrix R (see Section 4.6) was calculated and is shown below :

FILE VAL084.PRO-SENSITIVITY FNS (N=4).

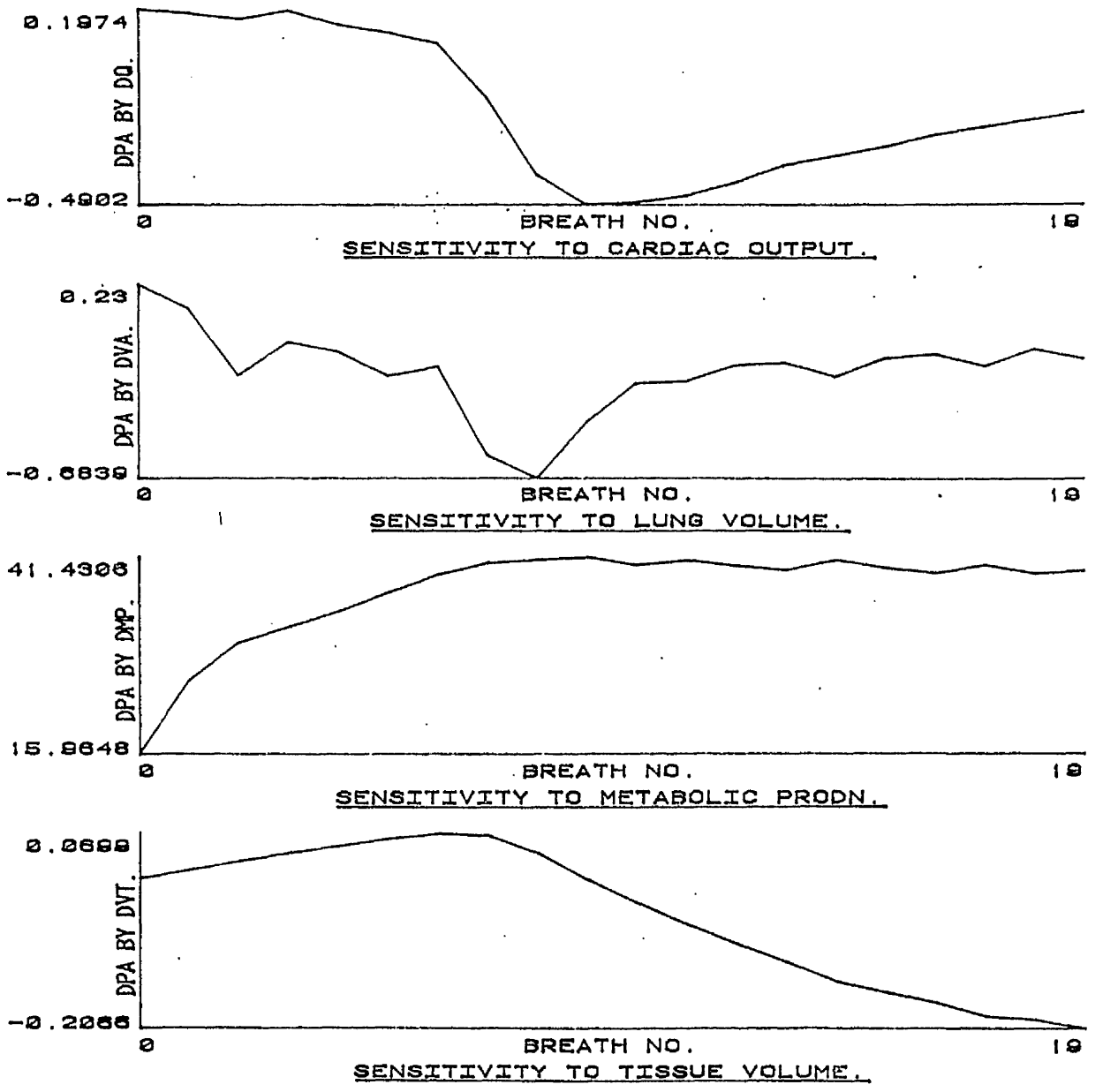
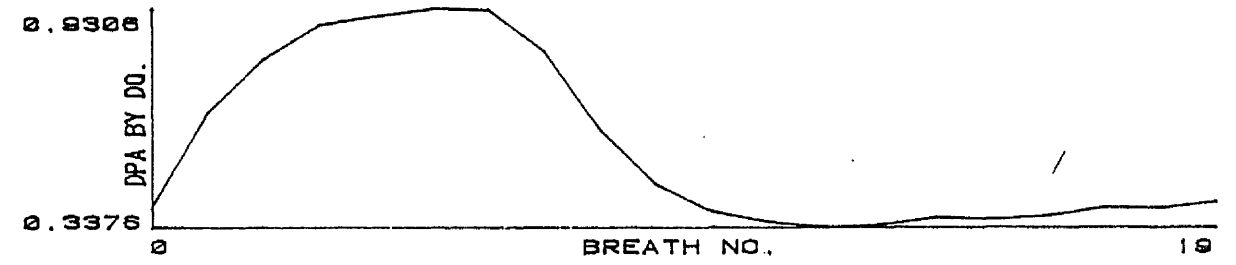
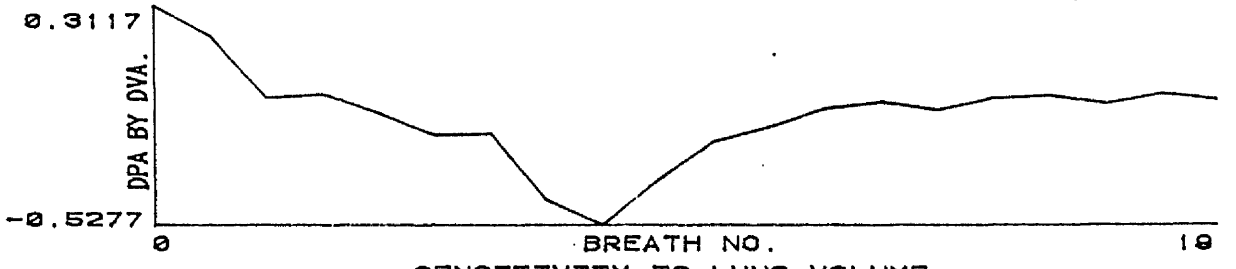


FIGURE 4·8

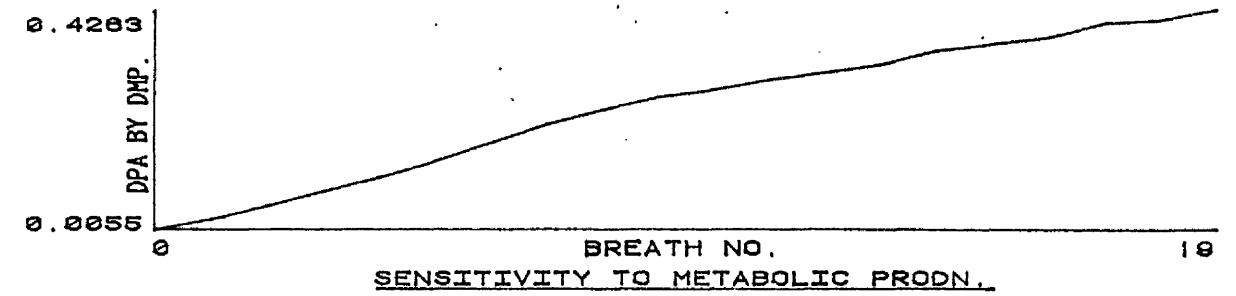
FILE VAL084.PRO-SENSITIVITY FNS (N=6).



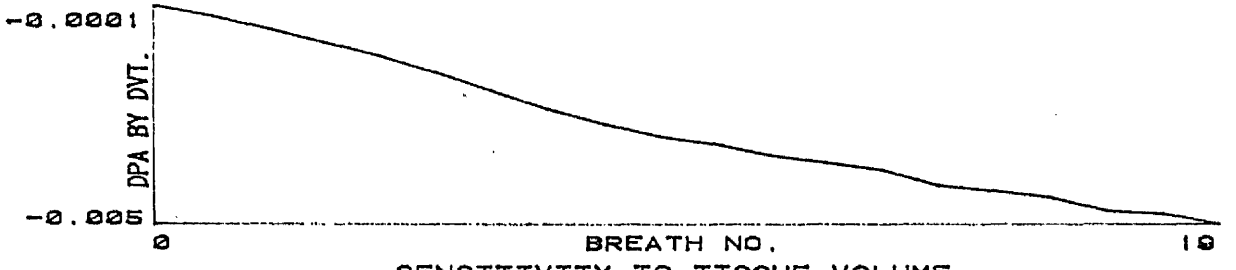
SENSITIVITY TO CARDIAC OUTPUT.



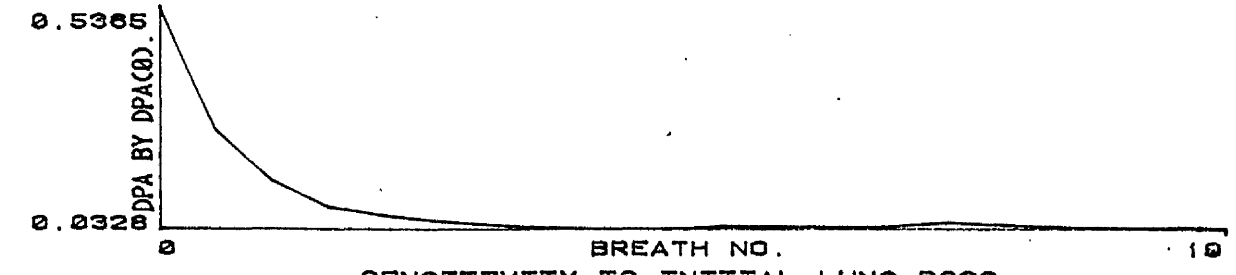
SENSITIVITY TO LUNG VOLUME.



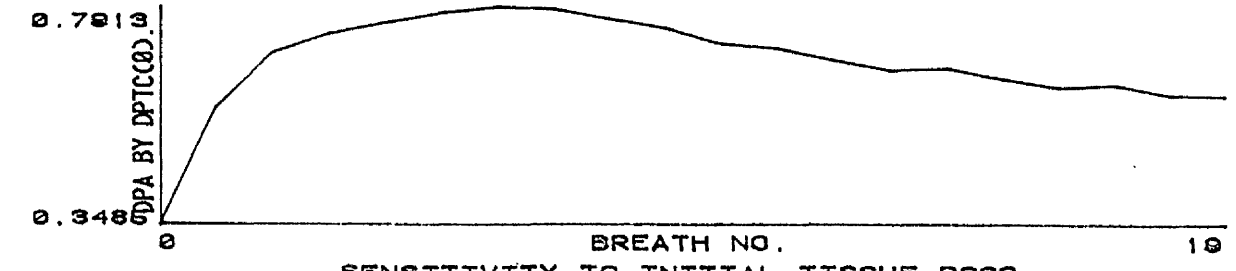
SENSITIVITY TO METABOLIC PRODN.



SENSITIVITY TO TISSUE VOLUME.



SENSITIVITY TO INITIAL LUNG PCO2.



SENSITIVITY TO INITIAL TISSUE PCO2.

FIGURE 4-9

FILE VAL141.PRO-SENSITIVITY FNS (N=4).

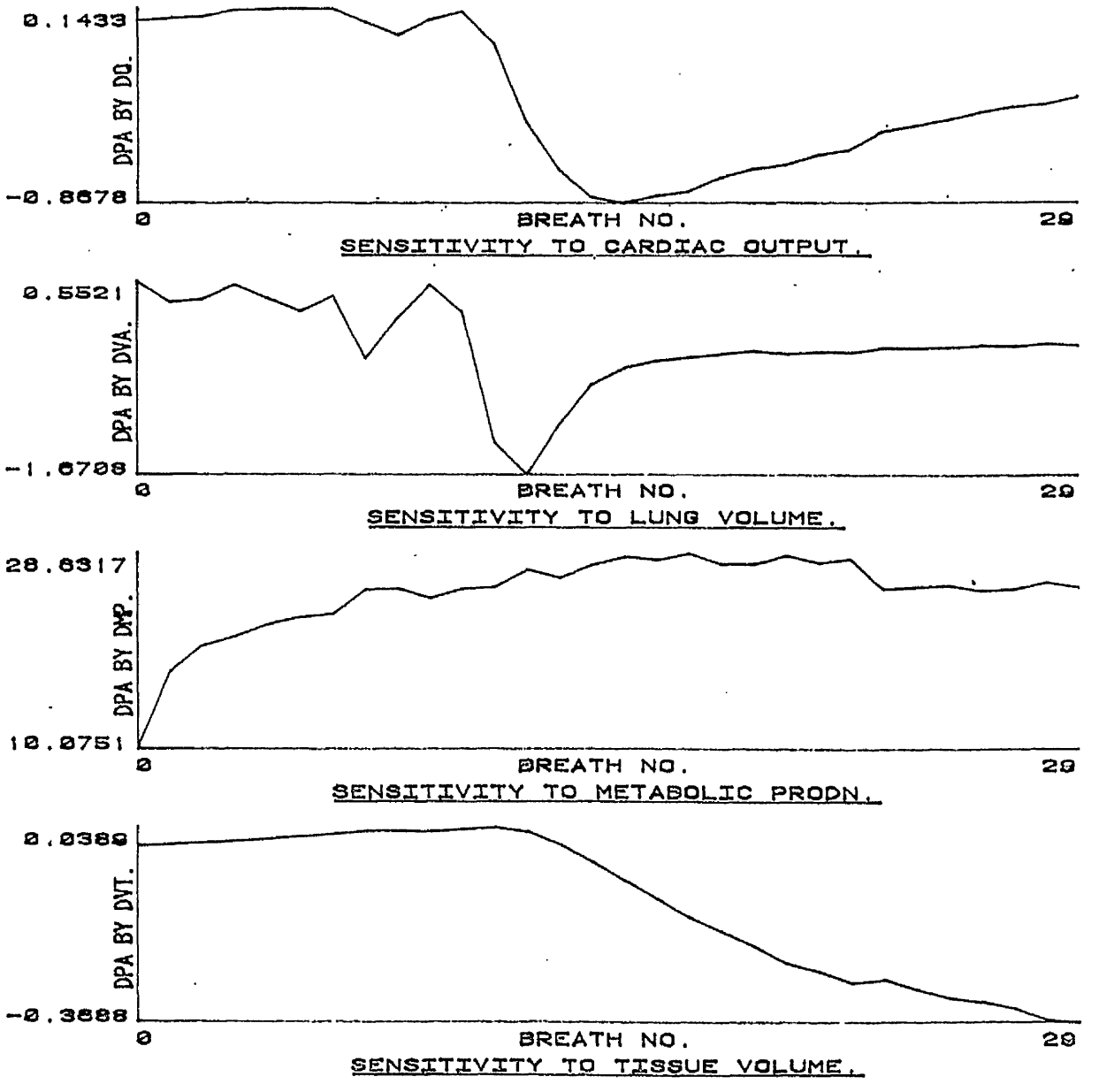
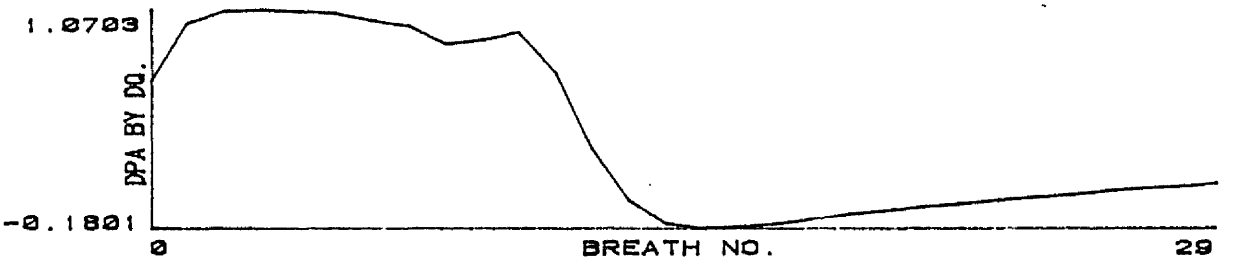
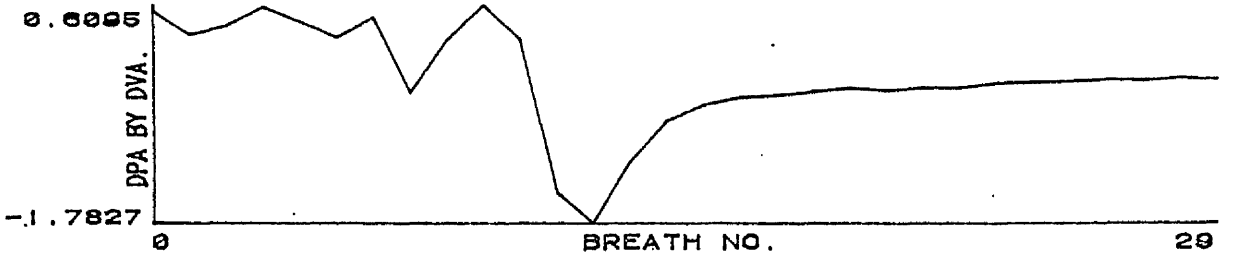


FIGURE 4·10

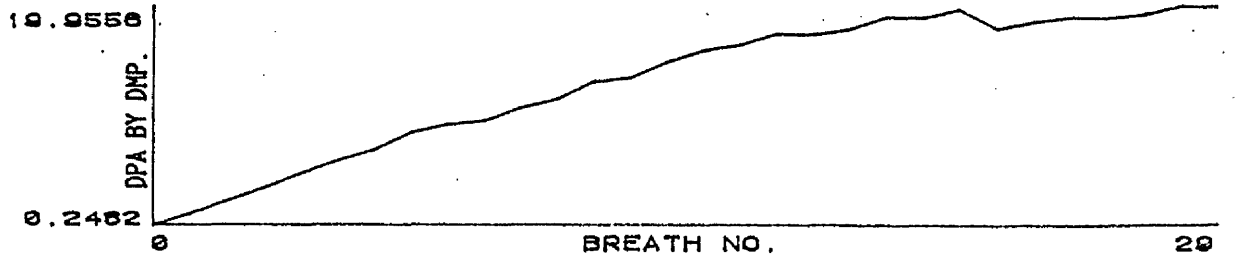
FILE VAL141.PRO-SENSITIVITY FNS (N=6).



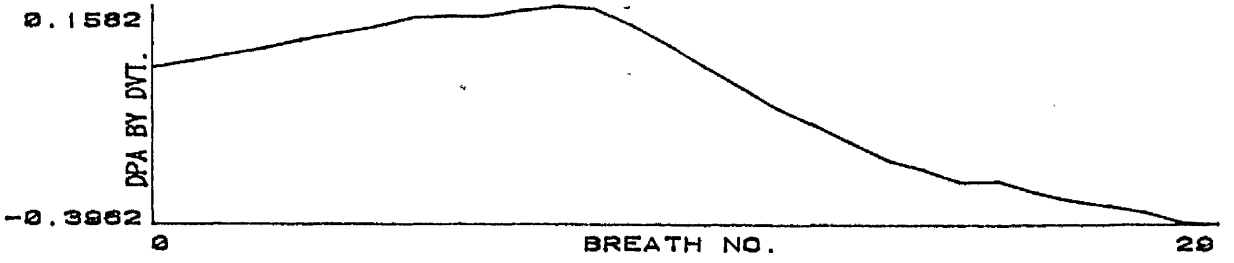
SENSITIVITY TO CARDIAC OUTPUT.



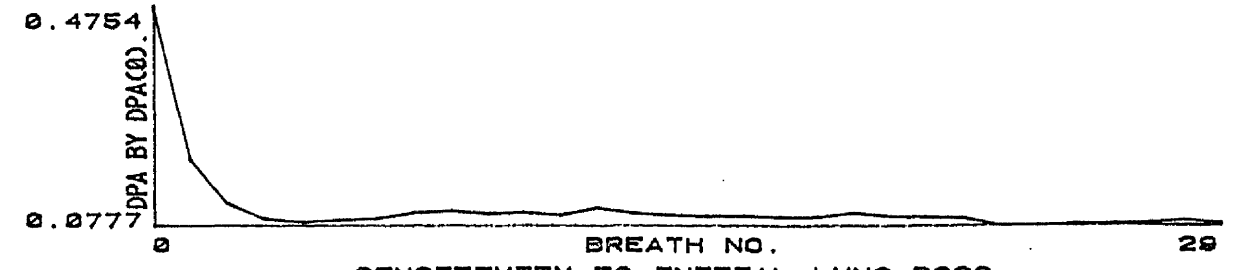
SENSITIVITY TO LUNG VOLUME.



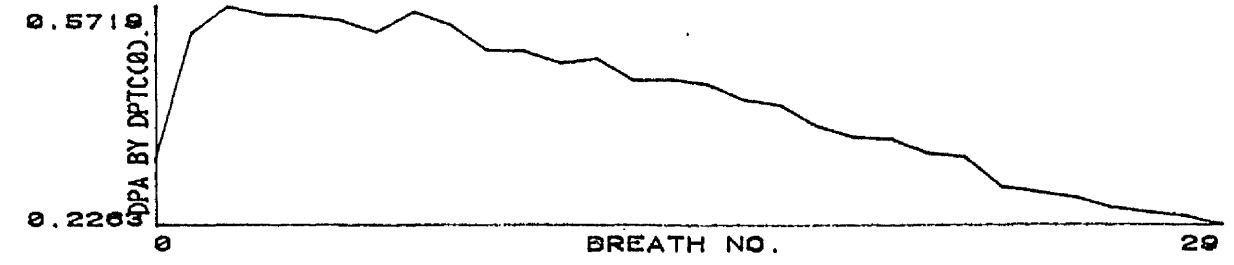
SENSITIVITY TO METABOLIC PRODN.



SENSITIVITY TO TISSUE VOLUME.



SENSITIVITY TO INITIAL LUNG PCO2.



SENSITIVITY TO INITIAL TISSUE PCO2.

FIGURE 4·11

	$\dot{Q}$	V_A	$\dot{M}$	V_{T_C}	$P_{A(0)}$	$P_{T_C(0)}$
$\dot{Q}$	1					
V_A	0.371	1				
$\dot{M}$	0.584	0.840	1			
V_{T_C}	0.581	0.841	0.999	1		
$P_{A(0)}$	0.090	-0.552	-0.190	-0.191	1	
$P_{T_C(0)}$	-0.952	-0.423	-0.712	-0.710	-0.199	1

Note the extremely large positive correlation between $\dot{M}$ and V_{T_C} (element 4,3 : 0.999) which indicates unidentifiability. This is to be compared with the corresponding correlation matrix for file VAL141 for which the correlation between $\dot{M}$ and V_{T_C}, although large (0.878), does not present unidentifiability problems

	$\dot{Q}$	V_A	$\dot{M}$	V_{T_C}	$P_{A(0)}$	$P_{T_C(0)}$
$\dot{Q}$	1					
V_A	-0.241					
$\dot{M}$	0.574	0.440				
V_{T_C}	0.267	0.528	0.878			
$P_{A(0)}$	0.149	-0.052	0.306	0.354		
$P_{T_C(0)}$	-0.781	-0.154	-0.904	-0.715	-0.483	1

The unidentifiability of VAL084 is also reflected in the determinant of the resultant parameter covariance matrix as compared to VAL141 for file VAL084 $\det \{ \text{cov} (\hat{\beta}) \}$ is 1.6×10^{4} while for file VAL141 it is 2.4×10^{-10} . It should be recalled these determinants are proportional to the volume of the respective confidence ellipsoids for each fit (Section 4.3, equation 4.26).

Further scrutiny of the parameter correlation matrices for the six parameter fits for all the other data files indicated that the $\dot{M}/V_{T_C}$ correlation was large (> 0.9) in almost every case.

(3) Examination of the parameter correlation matrices and the sensitivity curves for the six parameter fits indicates that a large negative correlation between $\dot{Q}$ and $P_{T_C(0)}$ is also prevalent (e.g. see the correlation matrices above). This factor coupled with the extremely large sensitivity of $P_{TC(0)}$ throughout the duration of the experiment (observable from the sensitivity curves), emphasises the inadvisability of assuming a steady-state (four parameter) model in general for this data.

The identifiability observations above tend to suggest that the model is over-parameterised. However, this contradicts the F-ratio tests and also the preceeding structural identifiability analysis does not give any reason to suspect global unidentifiability between $\dot{M}$ and V_{T_C} or $\dot{Q}$ and $P_{T_C(0)}$. This leads one, therefore to the inevitable conclusion that the unidentifiability is due to the form of experiment being poor rather than the nature of the model itself. This hypothesis is further confirmed by examination of Table 4.5. In this the actual sample variances and coefficients of variation are compared with those predicted on the basis of achieved fit, using the formulae derived earlier. The results are computed for the 'best' model as given by the F-ratio test. (Note also that the sample variances for the initial condition parameters $P_{A(0)}$ and $P_{T_C(0)}$ are not considered in this table since these are not expected to be time-invariant.)

In about 10/14 data sets it is apparent that the observed (sample) variances are considerably greater than those predicted on the basis of the

Table 4.5 : VALIDATION DATA

Average Predicted Variances ('Best' Model via F-Test) vs. Observed Sample Variances.

File		$\dot{Q}$	V_A	$\dot{M}$	V_{T_C}
VAL041	predicted	0.3	0.13	0.065	4.13
	actual	0.19	0.07	0.080	5.73
	CV(%)	2.9(8.2)	3.7	2.57	4.52
VAL05	predicted	0.36	0.28	large	large
	actual	0.0	0.25	large	large
	CV(%)	1.5(13.9)	8.4	>100	>100
VAL07	predicted	0.45	0.12	0.013	0.67
	actual	0.30	0.11	0.029	1.06
	CV(%)	4.4(0.08)	7.7	12.1	22.1
VAL08	predicted	0.37	0.40	large	large
	actual	0.67	1.50	large	large
	CV(%)	10.9(4.6)	79.5	>100	>100
VAL10	predicted	0.44	0.18	0.06	2.8
	actual	0.83	0.23	0.12	5.8
	CV(%)	10.5(6.6)	11.5	30.7	43.1
VAL11	predicted	0.67	0.21	0.05	1.6
	actual	1.06	0.71	0.04	1.9
	CV(%)	16.5(7.9)	37.5	16.7	33.1
VAL12	predicted	0.42	0.18	0.04	1.00
	actual	1.21	0.25	0.06	1.96
	CV(%)	29.3(5.1)	17.9	29.3	51.8
VAL14	predicted	0.28	0.16	0.02	0.75
	actual	0.76	0.27	0.07	2.39
	CV(%)	12.0(6.5)	14.6	21.6	33.4
VAL16	predicted	0.44	0.28	large	large
	actual	1.22	1.08	large	large
	CV(%)	17.8(3.6)	35.7	>100	>100
VAL17	predicted	0.85	0.28	0.10	4.6
	actual	0.94	0.76	0.06	1.43
	CV(%)	15.3(6.0)	29.1	16.9	19.7
VAL18	predicted	0.25	0.12	0.009	0.37
	actual	0.29	0.03	0.0125	1.17
	CV(%)	6.3(10.9)	1.7	5.7	30.6

cont'd.....

Table 4.5 : Cont'd.....

File		$\dot{Q}$	V_A	$\dot{M}$	V_{T_C}
VAL22	predicted	0.49	0.14	0.04	2.13
	actual	1.03	0.15	0.05	2.22
	CV(%)	16.5(4.1)	7.7	19.2	33.9
VAL23	predicted	0.39	0.21	large	large
	actual	0.86	0.83	large	large
	CV(%)	11.9(9.1)	30.6	>100	>100
VAL25	predicted	0.41	0.20	0.02	0.89
	actual	0.90	0.28	0.03	1.83
	CV(%)	14.9(8.1)	20.9	12.5	31.3
Average observed		12.2 %	21.9%	19.1% *1	34.3% *1
CV(%)		(6.8% dye)(2)			

Notes : (1) Unidentifiable files are not included in this average.

(2) Figure in brackets in this colum denotes values obtained from the dye-dilution experiments.

estimation results so that the Cramer-Rao lower variance bound is not achieved. However, the estimators used are asymptotically efficient. Therefore, one is forced to conclude that the form of test procedure used is not good enough to enable this asymptote to be reached.

4.9 Conclusions

On the basis of the above results it would seem that the deterministic and noise model structures used represent reasonably well the dynamics of homogeneous CO_2 gas transport. However, it is equally apparent that further investigation into the informational aspect of the problem is necessary.

What is really required is some form of test procedure which reduces the correlation between $\dot{Q}$ and the other parameters (especially the initial condition $P_{TC(0)}$) and produces estimates with smaller variance. Techniques for designing such an experiment will be discussed in Chapter 7.

CHAPTER 5

GENERALISED DESCENT METHODS FOR FUNCTION MINIMISATION

5.1 Introduction

As we have seen in Chapter 4, an important sub-problem of System Identification is that of Parameter Estimation. Central to the solution of this latter problem is the technique of Function Minimisation which in this context is concerned with finding the set of parameter values which minimise some distance measure between model and data.

Function Minimisation methods for estimating the parameters of the homogeneous CO_2 gas transport model have already been described by Pearson (234). However, the work at this stage was concerned with a three parameter model ($\dot{Q}$, $V_{A(0)}$, $\dot{M}$) and when the number of parameters was subsequently increased to four, five and then six parameters, the techniques recommended in (234) were found to be lacking. That is, they frequently failed to locate a minimum and sometimes crashed altogether. The reason for failure of these implementations was found to be almost entirely attributable to rounding error.

Concurrently with the author becoming involved in this project, new, numerically stable, Function Minimisation algorithms were beginning to appear in the literature, following the publication of the work on this topic by Gill et al (123, 125). These techniques were radically different from anything considered by Pearson (234) and an investigation of these more recent and efficient techniques was felt to be appropriate in order to tackle the more complex six parameter CO_2 gas transport model. Consequently, software was written by the author to implement these new techniques on the PDP11/45 computer and test these to assess their suitability for our particular problem. During this phase of the investigation it became apparent that this software, if configured in a sufficiently general manner, would be useful, not only in the context of the work described in this thesis, but in other projects both at the Department of Electronics and Electrical Engineering and at the Centre for Respiratory Investigation.

From these ideas the concept of the Function Minimisation package 'MINPAK' was born. A brief overview of this will follow in Section 8 of this chapter. (The package is described more extensively in Appendix B.) First, a review of the theory of unconstrained Function Minimisation will be given in order to describe the rationale behind the new numerically stable methods and in particular, those utilised in the 'MINPAK' package.

5.2 Function Minimisation - Introductory Concepts

The first systematic techniques for the solution of Function Minimisation problems go back as far as calculus. However, the arithmetic complexity of all but the most simple problems has been such that only with the coming of the era of the digital computer has their solution become feasible.

Minimisation problems can be split into two types :

(i) unconstrained problems in which the parameters are free to assume any values in parameter space,

(ii) constrained problems in which the parameters must lie in an admissable region in parameter space, e.g. such that certain functional relationships between the parameters remain satisfied.

The problem encountered in the work detailed in this thesis falls (or can be made to fall) into the former category.

The unconstrained problem can be stated mathematically as

$$\text{Find } \hat{\beta} : V(\hat{\beta}) = \min_{\text{w.r.t. } \beta} V(\beta) \qquad 5.1$$

That is, find the local minimum $\hat{\beta}$ of a non-linear scalar function $V(\beta)$ of an 'n' vector β . From the calculus, sufficient conditions for a solution of

equation 5.1 are :

$$\text{(i)} \qquad \| g(\hat{\beta}) \| = 0 \qquad 5.2$$

$$\text{(ii)} \qquad \beta H(\hat{\beta}) \beta^T \geq 0 \quad \text{for all } \beta \qquad 5.3$$

where $g(\hat{\beta})$ is the $n \times 1$ Jacobian gradient vector of 1st partial derivatives of $V(\beta)$ with respect to $\hat{\beta}$ and $H(\hat{\beta})$ is the symmetric $n \times n$ Hessian matrix of 2nd partial derivatives of $V(\beta)$ with respect to $\hat{\beta}$. Equation 5.2 implies that the Euclidean norm of the Jacobian gradient vector at the minimum be zero and equation 5.3 that the Hessian at the minimum be positive definite.

For most Function Minimisation problems of interest (e.g. model fitting), a closed form solution to the equation 5.1 is unavailable. Computer algorithms to solve the general unconstrained problem are thus iterative. An initial estimate $\beta^{(0)}$ of $\hat{\beta}$ is assumed and this is successively refined stage by stage in some manner, which allows the sequence of estimates generated $\{\beta^{(k)}\}$ to converge to $\hat{\beta}$. The minimum is deemed to have been located when some pre-specified criterion of convergence is satisfied, e.g. $[V(\beta^{(k)}) - V(\beta^{(k-1)})]$ or $\| \beta^{(k)} - \beta^{(k-1)} \|$ is small. Obviously the main factor characterising an algorithm is how the sequence of estimates $\{\beta^{(k)}\}$ is generated.

Nearly all the recent numerical algorithms to solve equation 5.1 have been what is termed descent methods : so called because they generate successive estimates which satisfy the inequality.

$$V(\beta^{(k+1)}) < V(\beta^{(k)}) \qquad 5.4$$

Methods which satisfy equation 5.4 are also said to be stable . Inequality 5.4 can be satisfied by modifying $\beta^{(k)}$ by the addition of a scalar multiple of the vector $p^{(k)}$ (usually termed a search direction in parameter space) which meets the condition

$$g^{(k)T}\ p^{(k)} < 0 \qquad 5.5$$

that is, for $p^{(k)}$ satisfying inequality 5.5 and given a sufficiently small scalar steplength $\alpha^{(k)}$, it can be shown (300, Chapter 2) that

$$V (\beta^{(k)} + \alpha^{(k)}\ p^{(k)}) < V (\beta^{(k)}) \qquad 5.6$$

Such a direction of search satisfying inequality 5.5 is said to be downhill. Linear search algorithms have been developed to choose a suitable steplength $\alpha^{(k)}$. These will be discussed in the next section.

5.3 Linear Search Techniques

Clearly there are many $\alpha^{(k)}$ satisfying inequality 5.5. The most obvious is to choose $\alpha^{(k)}$ such that it minimises $V (\beta)$ along direction $p^{(k)}$, i.e.

$$\alpha^{(k)} : V (\beta^{(k)} + \alpha^{(k)}\ p^{(k)}) = \min_{\text{w.r.t.}\ \alpha} V (\beta^{(k)} + \alpha\ p^{(k)}) \qquad 5.7$$

This was the method used in the earlier descent methods published in the literature (77, 114, 116). As is the case for equation 5.1, no closed form solution to equation 5.7 exists. However, a necessary condition is :

$$g (\beta^{(k)} + \alpha^{(k)}\ p^{(k)})\ \ p^{(k)} = 0 \qquad 5.8$$

Although choosing $\alpha^{(k)}$ such that equation 5.7 is satisfied at each stage theoretically, guarantees convergence of the descent algorithm, investigators found this to be computationally expensive. More recent numerical evidence has shown this procedure to be neither necessary nor desirable (92, 125). All that is required is to choose $\alpha^{(k)}$ such that $V (\beta)$ is sufficiently reduced along $p^{(k)}$ at each stage. Gill et al (125) recommend choosing $\alpha^{(k)}$ such that

$$\left| g\left(\beta^{(k)} + \alpha^{(k)} \, p^{(k)} \right)^T p^{(k)} \right| < -\eta \; g^{(k)^T} p^{(k)} \qquad 5.9$$

η is a scalar parameter in the range $[0, 1]$ fixed in advance determining the accuracy of the linear search. A small value of η will imply a high accuracy linear search whilst a larger value will imply a low accuracy linear search. Dixon (92) show that it is necessary to impose another condition on $\alpha^{(k)}$ to render the resultant algorithm theoretically convergent, namely that it should satisfy :-

$$V^{(k)} - V^{(k+1)} > - \alpha^{(k)} \, \mu \, g^{(k)^T} p^{(k)} \qquad 5.10$$

(μ is a small positive scalar ($\approx 10^{-4}$ typically).

Various techniques for successively refining $\alpha^{(k)}$ along $p^{(k)}$ (such that equations 5.7 or 5.9 and 5.10 are satisfied) have been suggested. The procedure most generally adopted is to approximate $V\left(\beta^{(k)} + \alpha \, p^{(k)} \right)$ (called $F(\alpha)$ below) by a polynomial of low order, usually degree two or three. These latter approximations are known respectively as quadratic and cubic interpolation.

In quadratic interpolation, the stationary point $\hat{\alpha}$ of the second order polynomial passing through three points is given by :-

$$\hat{\alpha} = \tfrac{1}{2} \; \frac{(\alpha_2^2 - \alpha_3^2) F_1(\alpha) + (\alpha_3^2 - \alpha_1^2) F_2(\alpha) + (\alpha_1^2 - \alpha_2^2) F_3(\alpha)}{(\alpha_1 - \alpha_3) F_1(\alpha) + (\alpha_3 - \alpha_1) F_2(\alpha) + (\alpha_1 - \alpha_2) F_3(\alpha)} \qquad 5.11$$

where α_1 , α_2 , α_3 are the steps along $p^{(k)}$ at which the function is evaluated and $F_1(\alpha)$, $F_2(\alpha)$ and $F_3(\alpha)$ are the respective function values.

In cubic interpolation, two function values and two derivatives with respect to α are necessary to define the stationary point. In this case, $\hat{\alpha}$ is given (assuming $\alpha_1 < \alpha_2$) by :-

$$\hat{\alpha} = (\alpha_1 - \alpha_2)\left\{1 - \frac{(g_2(\alpha) + \gamma + \eta)}{(g_2(\alpha) - g_1(\alpha) + 2\gamma)}\right\} \qquad 5.12$$

where $$\gamma = \sqrt{(\eta^2 - g_1(\alpha)\, g_2(\alpha))} \qquad 5.13$$

and $$\eta = \frac{3(F_1(\alpha) - F_2(\alpha))}{(\alpha_2 - \alpha_1)} + g_1(\alpha) + g_2(\alpha) \qquad 5.14$$

This interpolating formula was first derived by Davidon (77). Practically it is usual to use the above interpolating formulae iteratively. The function is evaluated at the new point $\hat{\alpha}$, and in the next iteration (assuming the convergence criteria are not satisfied) the points corresponding to the lowest function values are used. It may transpire that the new set of points no longer bracket the minimum. (i.e. extrapolation is required). Here neither formula 5.11 or formulae 5.12, 5.13, 5.14 can be relied upon. In this situation a linear search algorithm, to be reliable, must be safeguarded to ensure an $\hat{\alpha}$ is not predicted far outside the region of valid approximation for the interpolating formulae.

In practice, the assumption that the function $F(\alpha)$ is unimodal is also generally invalid. (Non-unimodality is not just limited to pathological functions since analytically unimodal functions may be non-unimodal when represented computationally). It is undesirable for algorithms to fail in this way and thus practical linear search algorithms must have some provision to deal with such a possibility. Practical considerations also mean that an empirical choice has to be made of the points at which the initial function (and derivative) values necessary to 'start-up' the algorithm should be evaluated.

From the above discussion it is evident that it is necessary to build various heuristic devices around the interpolating formulae 5.11 and 5.12, 5.13, 5.14 to create a reliable, practical algorithm. However, it is

inappropriate to discuss these in this introductory treatment. The particular linear search algorithm used in the MINPAK package is described in Appendix B .

5.4 Introduction to Descent Methods

Nearly all the descent methods published in the literature are based on the Taylor series expansion of $V(\beta)$ around the current point.

$$V(\hat{\beta}) = V(\beta+\Delta\beta)$$
$$= V(\beta)+g(\beta)^T\Delta\beta+\tfrac{1}{2}\Delta\beta^T H(\beta)\Delta\beta^T$$
$$+ \text{Higher order terms in 3rd, 4th , etc. derivatives} \qquad 5.15$$

The terms to the right of $V(\beta)$ on the right hand side of equation 5.15 may be looked on as a scalar correction to the function value at β say, to yield the function value at the minimum $\hat{\beta}$. Descent methods which truncate this series at the first term (i.e. $g^T\Delta\beta$) are generally known as First Order Methods. Those truncating the series at the second term (i.e. $\frac{1}{2}\Delta\beta^T H(\beta)\Delta\beta$) are known as Second Order Methods . Methods utilising derivatives of order higher than two have not been used in practical Function Minimisation techniques.

The basic first order method is called the method of steepest descent. It calculates the search direction $p^{(k)}$ using the negative of the gradient.

$$p_{SD}^{(k)} = -g^{(k)} \qquad 5.16$$

Equation 5.16 represents a locally optimal strategy relative to the current approximation since this is the direction in which $V(\beta)$ decreases most rapidly. However, in a global context, investigators have found this method to

be very inefficient in the region of the minimum.

Performance of the steepest descent algorithm can be improved by suitably transforming the parameters so that equal changes in the parameters effect equal changes in $V(\beta)$. Such Parameter Scaling is usually restricted to linear transformations of the parameters of the form

$$\beta_{SC} = D_{\beta} + v \qquad 5.17$$

where D is a constant diagonal matrix and v a vector constant. The precise nature of the scaling used in the MINPAK package will be discussed later.

The basic second order method is known as the Newton-Ralphson or Newton method. In this method successive search directions are generated using the following formula.

$$p_N^{(k)} = - H^{-1(k)} g^{(k)} \qquad 5.18$$

For a quadratic function the second order increment is exact since H does not depend on β . Therefore, theoretically, the Newton method will minimise a quadratic function in one step. The ability of a minimisation method to yield the minimum of an arbitrary quadratic function in a finite number of steps ' n ' is known variously in the literature as quadratic convergence, quadratic termination or following Fletcher (111), Property Qn. Thus, according to Fletcher's terminology, the Newton method possesses property Q1. For non-quadratic functions the second order increment will not be exact, although as the minimum is neared and terms involving third and higher order derivatives become small, $V(\beta)$ for well-behaved functions will become more amenable to approximation by a 'quadratic model'.

There are two main disadvantages which have been levelled at the Newton method.

(i) It requires the Hessian matrix to be known and inverted at each iteration - this can be a time consuming and frequently numerically unstable process.

(ii) In order for the Newton algorithm to be stable (in the sense defined by inequality 5.4) it is necessary that the Hessian matrix H be positive definite at each iteration - there is no guarantee this will be true for arbitrary general functions when H is evaluated at a point other than the minimum.

Due to the above deficiencies the Newton method has nowadays been largely superceded by a method originally due to Davidon (76) and since generalised into a class of methods by Broyden (50). These methods are known as Variable Metric or Quasi-Newton methods and have been proved considerably superior to all other general methods for unconstrained Function Minimisation. Since it is a particular implementation of these methods which has been used in the MINPAK package, these methods will now be discussed in some detail.

5.5 Quasi-Newton Methods

The requirement of the Newton algorithm that the Hessian be evaluated explicitly at each iteration is obviously a hinderance in practical computational problems. It would be far more useful if an algorithm could be found which, whilst still effectively utilising the properties of the second order increment, did not require explicit second derivative information. In addition, it is also essential that such an algorithm be stable.

The first algorithm fulfilling these requirements was that due to Davidon (76), but it awaited the definitive presentation of Fletcher and Powell (114) before receiving widespread recognition. For this reason the algorithm

is generally known as the Davidon - Fletcher-Powell (DFP) method. This method, instead of explicitly evaluating and inverting the Hessian at each iteration as in the Newton method, adopts a strategy of generating an approximation to the inverse Hessian and successively updating it over a number of iterations utilising only gradient information.

The algorithm is such that the approximation matrix S tends to H^{-1} at the minimum and possesses property Qn. In addition Fletcher and Powell (114) show that, provided the initial approximation matrix $S^{(0)}$ is chosen positive definite, theoretically the method is unconditionally stable under exact linear search (i.e. steplength $\alpha^{(k)}$ chosen according to equation 5.7).

The iterative scheme for choosing search vectors is

$$p_{QN}^{(k)} = - S^{(k)} g^{(k)} \qquad 5.19$$

$S^{(k)}$ being the approximation to the inverse Hessian at the kth iteration (compare with equation 5.18). Obviously the method is highly dependent on the algorithm used to update S at each iteration. In the DFP algorithm $S^{(k)}$ is updated at each stage by the addition of a correction matrix of rank two.

$$S^{(k+1)} = S^{(k)} + C^{(k)} \qquad 5.20$$

where $C^{(k)}$ is a specified matrix of rank two. It transpires that the DFP modification is not unique, as noticed by Broyden (50). In fact, the DFP update is only one member of a class of symmetric updating formulae which ensure that some properties of $S^{(k)}$ approximate those of $H^{-1(k)}$ at each iteration and exhibit property Qn with exact linear search. This class of methods is known as Variable Metric or more frequently Quasi-Newton methods (83). The key unifying factor between these methods is that they satisfy the following equation.

$$S^{(k+1)} \left(g^{(k+1)} - g^{(k)} \right) = \beta^{(k+1)} - \beta^{(k)} \qquad 5.21$$

This formula is referred to as either the Hereditary Property (1) or the Quasi-Newton Condition (213). For small $|| \beta^{(k+1)} - \beta^{(k)} ||$ this formula can be interpreted as the backward finite difference formula for $H^{-1(k+1)}$ along $p^{(k)}$, thus ensuring that at least along this direction, $S^{(k+1)}$ has some similarity to $H^{-1\,(k+1)}$. This makes the 'Quasi-Newton' interpretation self evident.

For the DFP method the correction matrix C is computed as follows

$$C^{(k)}_{DFP} = \frac{b^{(k)}\, b^{(k)T}}{b^{(k)T}\, y^{(k)}} + \frac{S^{(k)}\, y^{(k)}\, y^{(k)T}\, S^{(k)T}}{y^{(k)T}\, S^{(k)}\, y^{(k)}} \qquad 5.22$$

where $$b^{(k)} = \beta^{(k+1)} - \beta^{(k)} \qquad 5.23$$

and $$y^{(k)} = g^{(k+1)} - g^{(k)} \qquad 5.24$$

The first term on the right-hand-side of equation 5.22 is that which ensures that the generated sequence of approximation matrices tends to H^{-1} and the second term is that which ensures stability.

The theory of the quadratic termination properties (i.e. property Qn) of the DFP update depends critically on an exact linear search (114). As has been discussed in Section 5.3, exact linear search is computationally expensive. Thus in the late 1960's investigators (e.g. Broyden (51)) began to look around for an updating formula which did not depend quite so critically on an exact linear search. This resulted in the following.

$$C_{RK1}^{(k)} = \frac{(b^{(k)} - S^{(k)} y^{(k)})(b^{(k)} - S^{(k)} y^{(k)})^T}{y^{(k)T}(b^{(k)} - S^{(k)} y^{(k)})} \qquad 5.25$$

This update is known as the Rank-One update since the correction to the approximating matrix is of single rank. Davidon (77) and Murtagh and Sargent (215) have constructed algorithms based on equation 5.25. However, an unfortunate aspect of this update is that stability cannot be guaranteed.

In 1970, still seeking an algorithm less sensitive to the accuracy of linear search than the DFP update, Fletcher (112) proposed the following updating formula.

$$C_{BFGS}^{(k)} = -\frac{b^{(k)} y^{(k)T} S^{(k)}}{b^{(k)T} y^{(k)}} - \frac{S^{(k)} y^{(k)} b^{(k)T}}{y^{(k)T} b^{(k)}} + \left(1 + \frac{y^{(k)T} S^{(k)} y^{(k)}}{y^{(k)T} b^{(k)}}\right) \frac{b^{(k)} S^{(k)T}}{y^{(k)T} b^{(k)}} \qquad 5.26$$

The same updating formula was also discovered at the same time, independently, by Broyden (52, 53), Goldfarb (130) and Shanno (258). It is thus known as the Broyden-Fletcher-Goldfarb-Shanno (BFGS) or Complementary DFP update. The latter term stems from the property of this update that if H^{-1} say is updated using the BFGS formula, this corresponds to using the DFP formula to update H itself. (This result can be proved by applying the Matrix Inversion Lamma (300, Appendix F) to equation 5.26 .) Hence the DFP and BFGS updates may be considered duals in this sense.

Although the DFP and BFGS updates can be shown to be theoretically stable provided the initial approximation matrix $S^{(0)}$ is chosen positive definite, this , as was found by investigators (e.g. (51)), was not always borne out in practice due to rounding error. This was in fact the problem with earlier

applications of Quasi-Newton methods to the CO_2 gas exchange model estimation, as discussed in Section 5.1.

Various 'ad hoc' strategies have been suggested to overcome this problem (204a). However, these have been such that much good information built up in the approximating matrix is lost along with the bad when the 'ad hoc' adjustment to S is made.

The first really efficient method suggested to overcome the adverse affects of rounding error was that of Gill et al (123, 125), as was referred to in Section 1. This will, therefore, be described in the succeeding section.

5.6 Factorised Quasi-Newton Methods

Methods based on the approach outlined by Gill et al (123, 125) have come to be called Factorised Quasi-Newton methods. In contrast to traditional Quasi-Newton implementations these methods update a positive definite approximation to the Hessian itself rather than an approximation to the inverse Hessian. The search direction is then calculated by solving the set of linear equations defined by

$$B^{(k)} \; p_{QN}^{(k)} = - \; g^{(k)} \qquad 5.27$$

$B^{(k)}$ being the approximation to the Hessian at the kth iteration. Gill and Murray (123) show that $B^{(k)}$ can be recurred in factorised form, i.e.

$$B^{(k)} = L^{(k)} \; D^{(k)} \; L^{(k)T} \qquad 5.28$$

where $L^{(k)}$, a unit lower triangular matrix, and $D^{(k)}$, a diagonal matrix are the Cholesky Factors (297). Given $B^{(k)}$ in this form, equation 5.27 can be quickly and efficiently solved for $p^{(k)}$ using successive forward and backward

substitution (297).

The reason for recurring $B^{(k)}$ in factorised form is that one can make use of the highly stable numerical methods based on triangular systems to update the matrix factors L and D . These methods can be made to guarantee positive definiteness of the updated matrix $B^{(k+1)}$, irrespective of incurred rounding error. In addition, in the event of a near singular $B^{(k)}$, this positive definiteness is maintained in a 'minimal' manner, i.e. so that the least amount of information built up in $B^{(k)}$ from previous iterations is lost.

By applying the Matrix Inversion Lemma (300, Appendix F) to a rank two or rank one correction for H^{-1} (e.g. equations 5.22, 5.25 or 5.26) it can be shown (123) that the corresponding correction for H can be written in the form

$$B^{(k+1)} = B^{(k)} + \pi_1 z^{(k)} z^{(k)T} + \pi_2 \omega^{(k)} \omega^{(k)T} \qquad 5.29$$

where the scalars π_1 , π_2 and the vectors $z^{(k)}$ and $\omega^{(k)}$ are chosen to satisfy the Quasi-Newton update being used. Particular values for the DFP, RK1 and BFGS updates are given in Appendix F.

Having expressed the Quasi-Newton updating formula in the form given by equation 5.29, the next requirement is to be able to recur $B^{(k)}$ in factorised form without explicitly carrying out a Cholesky Factorisation at each stage. Gill and Murray, in their original paper (123) give two methods of doing this based on the addition of a symmetric matrix of rank one. (It is thus necessary to carry out their recommended procedures twice for Rank-Two Quasi-Newton updates). One of these methods, referred to in (123) as Method A, will be outlined below since this is the one which has been implemented by the author in the MINPAK package.

Consider the update

$$B' = B + \sigma z z^T \qquad 5.30$$

where B is available in factorised form as $L D L^T$ and it is required to obtain the updated matrix B' in the same form. After some manipulation, equation 5.30 can be written as

$$B' = L D^{\frac{1}{2}} A A D^{\frac{1}{2}} L^T \qquad 5.31$$

The idea underlying this method is now to successively reduce the matrix A to lower triangular form by orthogonal triangularisation (297). This involves successively post-multiplying A by a series of elementary Hermetian matrices W such that we get

$$\hat{L} = A W_1 W_2 \ldots\ldots W_{n-1} \qquad 5.32$$

in 'n - 1' multiplications, where $\hat{L}$ is lower triangular. Thus we now have

$$B' = L D^{\frac{1}{2}} \hat{L} \hat{L}^T D^{\frac{1}{2}} L^T \qquad 5.33$$

it can be shown that

$$D^{\frac{1}{2}} \hat{L} = \tilde{L} D^{\frac{1}{2}} \qquad 5.34$$

where $$D'^{\frac{1}{2}} = \gamma D^{\frac{1}{2}} \qquad 5.35$$

γ is also a diagonal matrix. Combining equations 5.33, 534 and 5.35 we then get

$$B = L \tilde{L} D' \tilde{L}^T L^T \qquad 5.36$$

Since the product of two lower triangular matrices is also lower triangular the required updated triangular matrix L' is obtained in this manner.

5.7 Modifications of Quasi-Newton Methods to Accept Finite Difference Gradient Modifications

So far it has been assumed that the analytical gradients are explicitly available in Quasi-Newton methods. However, finite difference gradient approximations may also be used in Quasi-Newton algorithms provided care is exercised in exactly how this is done (since as the minimum is approached $\| g \|$ tends to zero).

The two most common finite difference formulae used are forward differences and central differences. In forward differences the i^{th} element of the gradient vector is approximated :-

$$\frac{\partial V(\beta)}{\partial \beta_i} \approx \frac{V(\beta + h_i e_i) - V(\beta)}{h_i} \qquad 5.37$$

The analagous expression for central differences is :-

$$\frac{\partial V(\beta)}{\partial \beta_i} \approx \frac{V(\beta + h_i e_i) - V(\beta - h_i e_i)}{2 h_i} \qquad 5.38$$

where e_i is the unit vector along the i^{th} co-ordinate direction and h_i is the scalar perturbation along this direction. The first formula requires less function evaluations whilst the second is more accurate.

The biggest dilemma in using finite difference gradient approximations lies in the choice of an appropriate scalar perturbation parameter h_i . The analyst is faced with the competing requirements of high accuracy and low cancellation error. If h_i is too large the truncation error in the difference approximation is large and hence the gradient is inaccurate. Alternatively, if h_i is made too small, the cancellation error becomes large and the error in updating $S^{(k)}$ (or $B^{(k)}$) becomes unacceptable.

Early attempts to utilise finite difference derivatives in Quasi-Newton methods exacerbated the tendencies of these algorithms at the time towards instability. Stewart (267) sought to overcome this by choosing $h^{(k)}$ (a vector of perturbations along each parameter direction) at each stage to balance truncation error against rounding error. The algorithm however is complicated. Gill and Murray (123) argue against Stewart's technique and show that maintaining a constant perturbation in the finite difference approximations at each stage is a more favourable strategy. Provided the problem has been suitably scaled, they recommend an h_i in the range

$$2^{-2/3\,t} \ll h_i \ll 2^{-t/2} \qquad 5.39$$

where 't' is the number of binary digits in the mantissa of the machine used. In the MINPAK package an h_i equal to $2^{-t/2}$ is used.

5.8 The MINPAK Package for Unconstrained Function Minimisation - Main Features and Organisation

This section describes the PDP-11 Interactive Package for unconstrained Function Minimisation, MINPAK, written by the author. This software was written in response to the needs identified in the introductory section of this chapter. These needs, it was felt, would be best served by the creation of a package rather than a 'one-off' programme.

The algorithms inherent in this package are based on the Factorised Quasi-Newton algorithms due to Gill et al (123, 125). At the time these algorithms were required for use in the project described in this thesis, a suitable software implementation of these was not readily available.

MINPAK has been written in modular form. It is mainly Fortran based and has been implemented to run in either single or double precision

on a DEC PDP11 under both the RT-11 and RSX-11M operating systems. Although the package utilises highly sophisticated algorithms, it has been written in such a manner as to make it easily usable by a relative layman in the area of Function Minimisation algorithms. In fact, the only assumptions made of prospective users are that they should be able to code a Fortran subroutine to evaluate their chosen function to be minimised for any set of input parameter values β and compile this under the host PDP-11 operating system. Other system tasks such as linking the compiled routine to the rest of the package are made invisible to the user by the package 'iterative link' which utilises the indirect command file facility available under the DEC RT-11 Version 3 and RSX-11 M operating system.

The package provides the interactive framework within which the users routine can be run. The user is thus freed from the task of writing routines to input starting parameter values, etc., and also routines to output the progress of the minimisation. Output is available in short print or optionally full print diagnostic format. The package allows the user the choice of three Quasi-Newton updating formulae - BFGS, RK1 or DFP. This is specified by the user during the interactive link. The package also provides a facility whereby data may be preprocessed prior to input to the minimisation algorithm. It does this by allowing the insertion of a user specific data pre-processing routine into the created programme during the interactive link. If this facility is not required, a dummy subroutine is inserted into the programme. This feature is useful for setting up user specific random access disc data file assignments, etc. for use by the users function evaluation routine.

As mentioned in Section 5.4, relative scaling of the parameters is a very important practical consideration in Function Minimisation problems.

In MINPAK, a form of scaling known as range-scaling is used which is a special case of equation 5.17. The scaled parameters are defined by :-

$$\beta_{sc} = \frac{\beta - \beta_{min}}{\beta_{max} - \beta_{min}} \qquad 5.40$$

where β_{max} is a vector of maximum parameters likely to be encountered and β_{min} a vector of minimum parameter values. Range-scaling has the effect of normalising the parameters. Since in practical problems ill-conditioning is mostly due to certain parameters being vastly different in magnitude, this form of scaling is generally helpful, although better scaling can be obtained from a knowledge of the diagonal elements of the Hessian at the minimum. Range-scaling, however, has the advantage of being less complex, i.e. all it requires of the user is the minimum and maximum parameters likely to be encountered in order to scale the problem reasonably.

This concludes discussion on MINPAK in the main body of this thesis. The package is discussed in much more detail and an indication of its performance on analytic test functions is presented, in Appendix B.

5.9 The GMOPT Programme for Estimating the Parameters of The CO_2 Gas Exchange Model

This section describes the key computational step in estimating the parameters of the CO_2 gas exchange model as described in Chapter 3. - the GMOPT programme. GMOPT consists basically of the MINPAK software together with application - specific routines written for function evaluation in the gas exchange model context.

The data preprocessing routine for GMOPT performs application orientated input and data file initialisation. It then reads in the first data block of the file, which is a 'header' block containing information passed by the programme PRODAT (see Chapter 3, Section 4), into the appropriate FORTRAN COMMON region for later use by the function evaluation routine. Finally, it carries out a pass of the data proper calculating four end-tidal markers for each breath in the file, which are again stored in COMMON. These markers are the sample numbers corresponding to the beginning and end of the model and data end-tidal regions over which model/data comparison is carried out (see Chapter 3, Section 3). This is done at this stage for efficiency purposes to avoid the unnecessary generation of this information at each function evaluation.

Function evaluation itself, in the context of this problem, is much more computer intensive than the trivial analytical example used to illustrate the MINPAK package in Appendix B. That is, it implicitly involves solution of the model equations 3.8 - 3.11 for the given set of parameters and using the true measured ventilation and PCO_2 as stored on the patient data file at each sampling instant. These equations are solved by Euler's method (numerical first order integration) using an integration step of 0.033 secs. For an experiment of two minutes duration this integration step corresponds to 3,600 data points, which means the numerical difference equations must be updated correspondingly 3,600 times. These equations must, therefore, be efficient and for this reason, in the operational version of GMOPT, have been coded in PDP-11 Assembly Language.

Memory limitations on the PDP-11/45 preclude all the data being permanently core resident during the minimisation procedure. Thus the

model equations must be solved, and the calculation necessary to effect the model/data comparison carried out, for one block of data before the next can be read in from disc. This also adds to the time necessary to complete a function evaluation since using FORTRAN level random access disc read statements, the PDP-11 Central Processor Unit (C.P.U.) is doing no useful work whilst the reading operation is being carried out. This situation can be overcome by taking advantage of the parallel transfer capabilities of the PDP-11 data bus. Utilising this facility, machine language level 'double-buffering' disc reading routines have been written which allow the idle time of the C.P.U., whilst executing GMOPT, to be cut down.

The timings below for a function evaluation using one of the validation files gives some indication of the speed improvement effect from using machine language implementation of the time sensitive GMOPT programme sections :

	Implementation	Time for One Function Evaluation (secs.)
(i)	ALL FORTRAN	9.0
(ii)	DOUBLE BUFFER READS + MACHINE LANGUAGE IMPLEMENTATION OF MODEL EQUATIONS	5.8

For the complete estimation process the time saving using the machine language routines will be between 5 and 15 minutes.

By numerical experiment it has been found the most efficient value to use for the linear search termination criterion parameter η (see equation 4, Appendix B) is 0.2 . Similarly, 1.0 has been found to be the best initial steplength to input to the linear search algorithm (see Appendix B.2).

For range-scaling purposes reasonable physiological maximum and minimum values of the parameters were chosen as in Table 5.1. Finally, a print out from the minimisation procedure involving a four parameter model (for a ninety second experiment data file (RPO 141.PRO) is shown in Table 5.2. This tells a typical tale in terms of the progress of the minimisation procedure on the validation data.. The region of the minimum in parameter space is reached fairly quickly. After this, however, progress is slow and it can be seen how quite large changes in the model parameter values change the criterion function very little, i.e. the hypersurface in parameter space is very flat. This is symptomatic of these short experiment datasets and further reinforces the contentions made in Chapter 4. Sections 8 and 9 concerning the poor informational nature of such experiments and the need for a more enlightened form of test signal in future trials.

TABLE 5.1

RANGE-SCALING IN THE GMOPT PROGRAMME

Parameter	Minimum Value	Maximum Value
Cardiac output ($\dot{Q}$)	2.0 L/M	9.0 L/M
Lung volume ($V_{A(0)}$)	1 L	11 L
Metabolic production ($\dot{M}$)	0.1 L/M	0.5 L/M
Tissue volume (V_{TC})	1 L	11 L
Initial Alveolar partial pressure ($P_{A(0)}$)	20 mm.Hg	50 mm.Hg.
Initial Tissue partial pressure ($P_{TC(0)}$)	30 mm.Hg	60 mm.Hg.

GMOPT

DATA FILE: RP0141.PRO

VD = 0.146 HB = 15.00 TH = 0.000001 ETA = 0.20 MU = 0.0001 STEP = 1.00 SB = 0.00434

	QDOT	VA	MP	VT	F(ERR)	ITER	
**INI	5.000	5.000	0.2000	5.000	11.05	1	***
***GM	4.851	4.437	0.2900	5.050	1.397	9	***
***GM	4.631	2.503	0.2729	5.024	0.7550	16	***
***GM	5.360	1.845	0.2701	5.451	0.6123	23	***
***GM	6.081	1.846	0.2732	3.892	0.5262	31	***
***GM	6.126	2.001	0.2719	4.094	0.4875	39	***
***GM	6.513	1.814	0.2682	3.456	0.4401	47	***
***GM	7.011	1.491	0.2652	3.284	0.4193	55	***
***GM	7.473	1.469	0.2682	3.329	0.4077	64	***
***GM	7.666	1.421	0.2686	3.229	0.4059	73	***
***GM	7.892	1.333	0.2685	3.198	0.4049	81	***
***GM	7.923	1.322	0.2685	3.201	0.4048	88	***
***GM	7.920	1.322	0.2685	3.207	0.4047	95	***
***GM	7.903	1.325	0.2683	3.217	0.4047	114	***

OPTIMUM PARAMETERS :-

7.90	1.32	0.268	3.22	0.405

PTO = 42.64

TIME TAKEN = 00:02:39

NUMBER OF ITERATIONS = 140

TABLE 5.2

CHAPTER 6

MINIMISATION METHODS FOR FUNCTIONS INVOLVING SUMS OF SQUARES

6.1 Introduction

In Chapter 5 generalised methods for Function Minimisation were discussed and in particular, the application of the Quasi-Newton methods for estimating the parameters of the CO_2 gas transport model. Generalised methods are characterised by the fact that they do not depend on structural knowledge of the function being minimised and therefore are applicable, in theory at least, to any form of problem. The reason for the use of such methods in the cardiac output project was primarily historical. In the earlier period of the research differing forms of function were used to indicate 'goodness of fit' between model and data (2.34, Ch. 5) and use of generalised methods was necessary to cope with this.

More recently, however, criterion functions used have tended to be of the sums of squares form, i.e.

$$V(\beta) = \sum_{i=1}^{m} \left(e_i(\beta) \right)^2 \qquad 6.1$$

In the literature specific function minimisation techniques have evolved to solve problems of this form which fully exploit their special structure. These are known as non-linear least squares methods.

In the context of the work described in this thesis, use of least squares techniques have potentially two advantages over generalised methods :-

(1) Since use of non-linear least squares methods generally involves explicit evaluation of the parameter sensitivity matrix X at each stage, all the important diagnostic information on the adequacy of fit of the estimated model (see Chapter 4) is available directly from the results of the minimisation process.

(2) They are apt to be faster (which is an important consideration in view of the envisaged use of longer experiments (therefore entailing longer data sets) in the cardiac output procedure (see Chapter 7)).

It was considerations such as these which led to the investigation and implementation by the author of one particular non-linear least squares method (124) for estimating the parameters of the CO_2 gas transport model. Theoretically, this method seems to overcome most of the traditional problems normally associated with earlier least squares techniques although it appears largely untested on real data-fitting problems. Before discussing this method however, it is appropriate to give a brief introduction to the non-linear least squares function minimisation problem.

6.2 Non-Linear Least Squares Function Minimisation - Introductory Concepts

For the special form of function given by equation 6.1, the gradient vector $g(\beta)$ and the Hessian matrix $H(\beta)$ can be written as :

$$g(\beta) = 2X^T(\beta)e(\beta) \qquad 6.2$$

$$H(\beta) = 2(X^T(\beta)X(\beta)+B(\beta)) \qquad 6.3$$

where $X(\beta)$ is the m x n Jacobian or sensitivity matrix, $e(\beta)$ the vector of residuals and

$$B(\beta) = \sum_{i=1}^{m} e_i(\beta)H_i(\beta) \qquad 6.4$$

$H_i(\beta)$ is the Hessian matrix of $e_i(\beta)$.

Recall from Chapter 5 that in Newton's method for Function Minimisation the search vector $p_N(\beta)$ can be given by the solution of the equation

$$H^{(k)} p_N = - g^{(k)} \qquad 6.5$$

In a least squares context, this can be written (using equations 6.2 and 6.3) as

$$(X^{T(k)} X^{(k)} + B^{(k)}) p_N = - X^{T(k)} e^{(k)} \qquad 6.6$$

To compute $H^{(k)}$ it is necessary to evaluate m x n 1st partial derivatives and in addition, $mn(n+1)$ 2nd. partial derivatives. Therefore, in this form, Newton's method for sums of squares is still computationally expensive. However, if the problem is a data fitting problem, as in our application, then by implication, the residuals e should be small otherwise the solution is of no value. Thus $\| B \|$ will be small compared to $\| X^T X \|$ and under such circumstances $X^T X$ appears an adequate approximation to H. This approximation forms the basis of the Gauss-Newton (Newton-Gauss, Gauss or Quasi-Linearisation) method. In this method the search direction p_{GN} is calculated from the equation

$$(X^{T(k)} X^{(k)}) p_{GN}^{(k)} = - X^{T(k)} e^{(k)} \qquad 6.7$$

For genuine 'small-residual' problems the Gauss-Newton method will ultimately converge at the same rate as Newton's method despite the fact it utilises only 1st derivative information. In the true Gauss-Newton method, the parameter vector is updated at each iteration using a unit step in the direction of search, i.e.

$$\beta^{(k+1)} = \beta^{(k)} + \alpha^{(k)} p^{(k)} \qquad 6.8$$

where $\alpha^{(k)}$ is 1. Such an increment, however, may predict a solution outside the range of valid 1st order approximation. By choosing a stepsize less than unity (either fixed in advance or calculated using a unidimensional search algorithm such as those described in Section 3 of Chapter 5). The domain of convergence may be increased (152).

Although this 'damped least squares' method is more reliable than the original Gauss-Newton method, it still cannot be regarded as satisfactory for realistic problems. For instance, if at some iteration, the sensitivity matrix X is rank deficient, then $H^{(k)}$ will be singular and consequently $p^{(k)}$ will be undefined. Alternatively $p^{(k)}$ may well be defined but $g^{(k)} p^{(k)}$ may be zero and thus a downhill step will be impossible. In either event, the method would fail.

The latter situation, at least, may be avoided by determining a direction of search which lies between $p_{GN}^{(k)}$ and $-g^{(k)}$ (analagous to the Quasi-Newton methods for generalised problems).

Such a strategy, in a least squares context, was proposed by Levenberg (183). He advocated updating $p^{(k)}$ using the equation

$$(X^{T(k)} X^{(k)} + \lambda^{(k)} I)\, p^{(k)} = -X^{T(k)} e^{(k)} \qquad 6.9$$

where I is the identity. By choosing $\lambda^{(k)}$ small in the above equation $p^{(k)}$ tends to a step in the Gauss-Newton direction, whilst for large $\lambda^{(k)}$ $p^{(k)}$ tends to a step in the direction of steepest descent. Thus in this scheme $p^{(k)}$ can always be made downhill by choosing $\lambda^{(k)}$ sufficiently large. Improvements to the original Levenberg method (183) have been proposed by Maraquandt (203) and more recently by Fletcher (113) and Meyer and Roth (207).

Computational experience with the non-linear least squares methods discussed so far (and especially the later refined variants of Levenberg's algorithm (183))have shown that if these methods are going to converge, they will do so rapidly. However, they do rely heavily on the Gauss-Newton approximation, i.e. the assumption that $X^{T(k)} X^{(k)}$ is similar to $H^{(k)}$. If this is not so, i.e. either $X^{(k)}$ is near singular or $|| e^{(k)} ||$ is large, these techniques may give negligible improvement in performance in comparison with the generalised Function Minimisation methods discussed in Chapter 5.

In the cardiac output estimation data, it is not inconceivable that such a condition may arise and it is necessary to be able to cater for this. In the context of least squares Gauss-Newton algorithms what is required is the ability to incorporate second derivative information into the algorithm in the least computationally expensive way (i.e. knowledge of the B matrix in equation 6.6) whilst retaining the basic Gauss-Newton structure where this is relevant. Such a method has in fact recently been published in the literature (124) and is discussed in the next section.

6.3 Gill and Murray's Non-Linear Least Squares Method

Gill and Murray's algorithm (124) is based on the singular value decomposition of the sensitivity matrix X (297). This allows X to be factorised in the form

$$X = U S V^T \qquad 6.10$$

U is an m x n matrix consisting of the first 'n' orthonormalised eigenvectors of $X X^T$ (an m x m matrix), V consists of the orthonormalised eigenvectors of $X^T X$ and S is a diagnonal matrix consisting of the non-negative square roots of the eigenvalues of $X^T X$. These are called the singular values and

can be arranged in descending order (i.e. $S_{i+1} < S_i$, $i = 1$, n) without loss of generality by appropriate row and column ordering of U and V . Such an ordering is assumed here. Using this decomposition, the Gauss-Newton direction can be computed as

$$p_{GN} = V\ S^{-1}\ U^T\ e \qquad 6.11$$

(The inversion of S is trivial since it is a diagonal matrix). Alternatively, the Newton step (corresponding to equation 6.6) can be computed by solving the following system of equations.)

$$(S^2 + V^T B V)\ z = - S\ U^T\ e \qquad 6.12$$

$$p_N = V z \qquad 6.13$$

(z in equation 6.12 is obtained via Cholesky factorisation ($L D L^T$) of $S^2 + V^T B V$ followed by successive forward or backward substitution). As the basis of a practical minimisation algorithm for least squares problems this scheme is unsatisfactory on two counts :

(1) $S^2 + V^T B V$ will generally be ill-conditioned hence causing numerical problems.

(2) The scheme effectively ignores the least squares structure of the problem.

However, suitably modified, equations 6.12 and 6.13 provide the basis of a radically new algorithm for non-linear least squares problems. An important property of the new algorithm is that the Gauss-Newton direction p_{GN} is obtained as an intermediate product in the computation of p_N which thus provides a natural way in which the Gauss-Newton step may be 'enhanced' if necessary.

The basic idea is to compute p_N as a sum of two components :

$$p_N = p_1 + p_2 \qquad 6.14$$

p_1 is calculated in the subspace spanned by the columns of V corresponding to the larger singular values and p_2 is calculated in the subspace corresponding to the smaller ones. Since the singular values are assumed arranged in S in descending order, this means partitioning S such that

$$S_2 = \text{diag}\ (S_1, S_2, S_3, \ldots\ldots S_r) \qquad 6.15$$

$$S_2 = \text{diag}\ (S_{r+1}, S_{r+2}, \ldots\ldots S_n)$$

Gill and Murray (124) define 'r' as the grade of the matrix X. This partitioning of S implies a corresponding partitioning of U and V. Applying this partitioning to equations 6.12 and 6.13 results in two coupled systems of linear equations which must be solved iteratively. However, utilising an approximation to this Gill and Murray (124) show that p_N may be calculated by solving the following set of equations.

$$p_1 = - V_1 S_1^{-1} U_1^T e \qquad 6.17$$

$$(S_2^2 + V_2^T B V_2)\ y = - S_2 U_2^T e - V_2^T B p_1 \qquad 6.18$$

$$p_2 = V_2 y \qquad 6.19$$

$$p_N = p_1 + p_2 \qquad 6.20$$

In contrast to $(S^2 + V^T B V)$, $(S_2^2 + V_2^T B V_2)$ in equation 6.18 is not ill-conditioned since, by implication it does not contain the larger singular values of S. Equation 6.18 can therefore be efficiently solved for y using $L D L^T$ factorisation methods. (Should $(S_2^2 + V_2^T B V)$ be indefinite, modified Cholesky factorisation (123a) may be used).

Note that in equation 6.17 if the grade 'r' of V is equal to its rank 'n' then p_1 is synonymous with the Gauss-Newton direction p_{GN} as

defined in equation 6.11. When the grade of X is less than 'n' p_1 is termed the graded Gauss-Newton direction. It can be thought of as the Gauss-Newton direction in the space spanned by V_1. By extending this argument p_2 can be thought of as the correction to the graded G-N direction required to ensure convergence where H is dissimilar to X^TX. Thus by this mechanism, second derivative information is incorporated into the Gauss-Newton algorithm where appropriate.

In the Gill-Murray method (124) the Gauss-Newton step is used (i.e. equation 6.17 which is equivalent to equation 6.11 for 'r' equal to 'n') until the progress of the algorithm falters. At this stage a corrected graded Gauss-Newton step (r less than n) is taken.

The rules recommended by Gill and Murray for grade changing are as follows :-

(1) The first time the decrease in function value falls below 1% reduce the grade 'r' so that the condition numbers of S_1 and S_2 are approximately balanced.

(2) After this, each time the decrease in function value falls below 1% reduce the grade by 1.

(3) Should the reduction in function value subsequently become greater than 10% again, increase the grade to 'n', i.e. revert to the original G-N step.

For the Gill-Murray scheme, knowledge of the matrix B is required. If second derivatives are available, these can be used explicitly. However, in our particular situation where formulating the gradients is costly enough (since this involves the solution of a co-system of differential equations) this approach is not viable. Thus second derivative information is obtained via finite differences. This is best done in the context of this particular algorithm

as follows :-

Defining an (n - r) matrix Y as

$$Y = V_2^T B^{(k)} \qquad 6.21$$

and an (n - r) x (n - r) matrix Q as

$$Q = Y V_2 \qquad 6.22$$

then equation 6.18 can then be written as

$$(S_2^2 + Q) y = - S_2 U_2^T e - Y p_i \qquad 6.23$$

Finite difference approximations to Y and hence Q can be calculated by differencing the sensitivity matrix X along the columns of V_2 . Partitioning V_2 by columns (there will be n - r of these), and Y by rows, utilising the first column of V_2 (V_1 say), a finite difference approximation to the first row of Y (y_1) is :

$$y_1 = v_1^T B^{(k)} = e^{(k)T} \left[X (\beta^{(k)} + \frac{h v_1}{h}) - X (\beta^{(k)}) \right] \qquad 6.24$$

where h is the interval for differencing and is chosen as discussed in Section 7 of Chapter 5.

Since the grade 'r' of the sensitivity matrix X is rarely significantly less than the rank of X, 'n', (since it is generally equal to the number of dominant singular values of S), this implies that the (n - r) gradient evaluations taken to compute Y and Q are generally few in number.

Software has been written by the author to implement the algorithm outlined in principle above. This software is similar in spirit to the MINPAK package discussed in the previous chapter and in Appendix B, and has been written in the same structured format. Collectively this software constitutes the NLSPAK package, intended for non-linear least squares problems, and is described in detail in Appendix C.

6.4 The NOLLS Programme for Estimating the Parameters of the CO_2 Gas Transport Model using the Non-Linear Least Squares Algorithm

The 'ad hoc' criterion suggested in Chapter 3 for model/data comparison is effectively a least squares criterion, as discussed in Chapter 4, and is thus amenable to minimisation by non-linear least squares methods. This approach requires that the sensitivity matrix X be explicitly available. Computing analytical sensitivity information involves the solution of an additional cosystem of ' 1 ' differential/difference equations for each parameter sensitivity sought in addition to the ' 1 ' model equations which it is already necessary to solve in order to compute the model output (281). Since in our application we have two model 'state' equations, the solution of the complete sensitivity cosystem for e.g. the six parameter model requires the numerical solution of an extra twelve simultaneous difference equations. Fortunately, the sets of sensitivity equations for the different parameters are of similar form and differ only in the 'coupling term' through which each sensitivity equation is dependent on the model state equations, there being no interaction among the sensitivity equations for the different parameters.

By differentiating the model equations 3.8 and 3.9 with respect to a parameter (β say) sensitivity equations of the following form are obtained (in both the 4,5 and 6 parameter case).

$$V_A \frac{d}{dt}\left(\frac{\partial P_A}{\partial \beta}\right) = \dot{V}\left(\frac{\partial P_I^*}{\partial \beta} - \frac{\partial P_A}{\partial \beta}\right) + \dot{Q}b\left(\frac{\partial P_{TC}}{\partial \beta} - \frac{\partial P_A}{\partial \beta}\right) + C_1(\beta) \qquad 6.25$$

$$b\, V_{TC} \frac{d}{dt}\left(\frac{\partial P_{TC}}{\partial \beta}\right) = -\dot{Q}b\left(\frac{\partial P_{TC}}{\partial \beta} - \frac{\partial P_A}{\partial \beta}\right) + C_2(\beta) \qquad 6.26$$

where $C_1(\beta)$ and $C_2(\beta)$ are the coupling terms with the state equations appropriate to the particular parameter β .

The full equations for each parameter $\dot{Q}$, V_A, $\dot{M}$, V_{TC}, $P_{A(0)}$,

$P_{TC(0)}$ (containing the specific coupling terms C_1 and C_2 and the initial conditions for the 4, 5 and 6 parameter model) are detailed in Appendix D.

The term $\frac{\partial P_I^*}{\partial \beta}$ in equation 6.25 is analagous to the P_I^* term in the model state equation 3.8 and takes a value dependent on the phase of the breath (see equation 3.11). Over the first deadspace of inspiration the term $\frac{\partial P_I^*}{\partial \beta}$ takes the value of the flow-weighted mean of that particular model sensitivity over the last deadspace of the previous expiration (analagously to equation 2.35a.)

These sensitivity equations are integrated numerically using Euler's method as is done for the model equations in Chapter 5.

To compute the elements of the sensitivity matrix X we actually require the sensitivities of the flow-weighted model output y_{mi} ($\equiv \overline{PCO_2}$ in equation 3.6). Therefore the elements of X must be calculated from the point by point model sensitivities $\frac{\partial P_{Ai}}{\partial \beta_j}$ over the model end-tidal region in a manner similar to equation 3.6. A listing of the 'RUN' subroutine which mechanises the above calculations is given in Appendix G.

From this listing it is evident that the function evaluation routine in NOLLS incurs substantially greater computational overhead than that for the GMOPT programme. The times for a single execution of each routine on a 2 minute file (using a 4 parameter model) are as follows :-

(1) GMOPT - 5.8 secs.

(2) NOLLS - 28.1 secs.

However, it has to be remembered in the latter case, gradient information is also being computed in the one pass of the data. Using equation C.8, which defines a fairer index of computational labour (300), we find that the time taken for GMOPT to compute similar information to NOLLS would be

29.0 secs. i.e. longer than NOLLS. Thus NOLLS is slightly more efficient in this respect and could be made more so by programming the difference equation solution code (SUBROUTINE MODELL-See Appendix G) in machine language as is done for GMOPT.

6.5 Incorporation of Scaling and Simple Constraint Handling into the NOLLS Programme

The use of range-scaling in the GMOPT programme, although adequate, was not entirely satisfactory. It was thus decided to further investigate this scaling problem in the context of the non-linear least squares algorithm to ascertain if any improvement could be affected.

On 'poor' data the condition number of the Hessian matrix $\underline{H}$ is large and this tends to make the angle of descent θ (i.e. the angle between the search vector p and gradient vector g) almost orthogonal. This causes problems in descent algorithms. The aim of scaling therefore is to reduce the condition number of H such that θ becomes small.

In the non-linear least squares case, the condition number of H is invariably reflected in that of $X^T X$. This can be conveniently examined in the case of the Gill-Murray algorithm (124) by examination of the singular values S computed in the singular value decomposition of X since these are the non-negative square roots of the eigen values of $X^T X$.

For the case of a typical validation file (VAL 252.TST) and a four parameter model the unscaled condition number of $X^T X$ was found to be greater than 10^9 , and the angle of descent θ greater than 89.5^o . For the same case using range scaling (with scaling factors as in Table 5.1) the corresponding condition number was only reduced to the order of 10^6 which is

disappointing.

It transpires that a better form of parameter scaling may be obtained for our particular problem by utilising the sensitivity information provided by the non-linear least squares algorithm. Since the Gauss-Newton step is given by :-

$$p = - \left[X^T X \right]^{-1} g \qquad 6.27$$

it is clear that the required diagonal parameter transformation matrix X (see equation 5.17) should be such that it results in a diagonal transformation matrix D_1 in $\left[X^T X \right]^{-1}$ such that

$$\left[X^T X \right]^{-1}_{SC} = D_1 \left[X^T X \right]^{-1} \longrightarrow I \qquad 6.28$$

Thus a diagonal matrix D_1 is required which is sufficiently similar to $X^T X$. A reasonable choice is to make D_1 equal to the diagonal elements of $X^T X$. The corresponding D which would result in such a D_1 is therefore defined by

$$d_i = \left(\frac{m_{ii}}{m}\right)^{\frac{1}{2}} \qquad 6.29$$

where 'm_{ii}' is the i, i^{th} element of $X^T X$ and 'm' is the number of observations in the experiment. This scaling factor can be thought of as a sort of 'root mean square sensitivity' for the whole experiment.

On the basis of examination of a large number of data sets, both from the 2 min validation experiments and the longer form of experiments to be discussed in Chapter 7, the scale factors chosen for NOLLS (on the basis of equation 6.29) were as shown in Table 6.1.

Using this form of scaling the condition number of $X^T X$ for the

TABLE 6.1

PARAMETER SCALING IN THE NOLLS PROGRAMME

Parameter	Scaling Factor d_i
Cardiac Output ($\dot{Q}$)	0.5
Lung Volume ($V_{A(0)}$)	0.33
Metabolic Production ($\dot{M}$)	0.05
Tissue Volume (V_{TC})	0.1
Initial Alveolar Partial Pressure ($P_{A(0)}$)	0.1
Initial Tissue Partial Pressure ($P_{TC(0)}$)	0.1

problem discussed earlier was reduced to of the order of 100 which was a considerable improvement over the range scaling case.

During preliminary numerical experiments on the validation files the least squares algorithm was found to fail frequently on ill-conditioned files in early iterations. Closer investigations found this to be due to large step-lengths being generated by the algorithm in these earlier iterations resulting in steps into negative parameter space being attempted with subsequent floating overflow in the 'RU N' routine. Rather than revert to a 'full-blown' Constrained Function Minimisation solution, a simple constraint handling algorithm was designed to overcome this problem resulting in only a small modification to the 'SEARCH' algorithm.

The idea is that a positive lower bound (LB) on each of the model parameters is specified . If at any time the steplength algorithm predicts a step $\alpha^{(k)}$ which would result in a parameter β_i being reduced below its lower bound LB_i , this situation is detected and the steplength $\alpha^{(k)}$ reduced accordingly so that the parameter is set equal to its lower bound value.

$$\alpha^{(k)}_{\text{reduced}} = \frac{LB_i - \beta_i}{p_i^{(k)}} \qquad 6.30$$

The whole parameter vector is then recalculated using this reduced steplength. The procedure is repeated until the following inequality is satisfied.

$$\beta_i^{(k+1)} \geqslant LB_i \qquad i = 1, 2, 3 \ldots\ldots n \qquad 6.31$$

This modification to the linear search algorithm was found to be adequate for constraining the problem in positive parameter space.

6.6 Comparison of the Relative Efficiencies of the GMOPT and NOLLS Programmes

Numerical experiments were undertaken to compare the performance in speed terms on different data sets under varying conditions (i.e. different number of parameters, experiment lengths, etc.) of GMOPT and NOLLS. This was to discern the best method to recommend for routine use in connection with the non-invasive cardiac output measurement technique at the Royal Infirmary. The results of these experiments are summarised in Table 6.2.

The timings for the GMOPT programme have been adjusted to allow for the fact that the local search algorithm undertaken at the end merely confirms the solution by subtracting the time taken to carry this out from the total time.

From these results, even although comparison is a bit difficult due to slightly different convergence criteria for the two algorithms it is immediately apparent that the 'NOLLS' programme is vastly superior in performance. Based on the limited number of results detailed in Table 6.2, it would appear to be about twice as efficient.

This improvement is not due to the function evaluation routine being effectively faster in the non-linear least squares case. In fact, the results in Table 6.2 suggest that the average computation time per function evaluation (i.e. total time divided by index of computation labour) is actually less in the case of 'GMOPT'. This would seem to be contrary to the timing comparisons presented in Section 4. However, this is only because these latter results also include an element of the inter-iteration computation time of the algorithm. This relatively larger inter-iteration computational burden of the 'NOLLS' programme is primarily due to the need to carry out a singular-

Data File	No. of Pars.	Expt. Length.	No. of Data Pts.	Time Taken (t) (GMOPT)	N_c	Time Taken (t) (NOLLS)	N_c
TEST 1 . PRO	6	10 mins	6,000	17 mins 56 sec	168	6mins 20 sec.	56
TEST 1 . PRO	4	10 mins	6,000	12 mins 32 sec	117	4 mins 42 sec.	40
REPO 11. PRO	4	9 mins	5,400	11 mins 19 sec	115	5 mins 43 sec.	50
REPØ 13. PRO	4	9 mins	5,400	9 mins 21 sec	96	4 mins 51 sec.	45
REPØ 14. PRO	4	9 mins	5,400	10 mins 50 sec	111	4 mins 23 sec.	40
RPØ 41. PRO	4	$1\frac{1}{2}$ mins	900	2 mins 29 sec	114	1 min 02 sec.	55
RPØ 42. PRO	4	3 mins	1800	5 mins 23 sec	167	2 mins 02 sec.	55
RPØ 43. PRO	4	$4\frac{1}{2}$ mins	2,700	4 mins 06 sec.	82	2 mins 20 sec.	40

TABLE 6.2

COMPARISON OF GMOPT AND NOLLS FOR DIFFERENT DATA SETS UNDER VARYING CONDITIONS

value decomposition at each stage, which is computationally expensive.

The increase in efficiency of the 'NOLLS' programme is mainly due to the superior approximation to the Hessian matrix H generated by the non-linear least squares algorithm over that of the Quasi-Newton algorithm. This results in a faster rate of convergence e.g. see the appropriate computer print-outs for the file RPO142.PRO for the NOLLS and GMOPT algorithm in Tables 6.3 and 6.4.

This improved convergence is perhaps better illustrated by Figure 6.1 which shows how the criterion function is reduced as a function of increasing index of computational labour for file RPO142.PRO for each algorithm.

Thus in summary, the non-linear least squares algorithm is recommended for routine use hereafter both on the basis of its increased efficiency and the fact that it allows us to provide statistical information about the paramter estimates so important to the model-fitting procedure without further computation.

6.7 Formulation of the Maximum Likelihood Estimation Method as a Sums of Squares Problem

In Chapter 4 it was mentioned that the maximum likelihood estimation technique could also be interpreted as a sums of squares F.M. problem. Hence this is also amenable to minimisation by the algorithms discussed in this chapter. The resultant programme is known as 'MAXL'.

Recall that in Chapter 4, in the maximum likelihood method, the model/data errors (i.e. the deterministic prediction errors) e are modelled in the form :

GMOPT

TABLE 6.3

DATA FILE: RP0142.PRO

VD = 0.146 HB = 15.00 TH = 0.000001 ETA = 0.20 MU = 0.0001 STEP = 1.00 SB = 0.00434

	QDOT	VA	MP	VT	F(ERR)	ITER	
**INI	5.000	5.000	0.2000	5.000	15.17	1	***
***GM	4.984	4.624	0.2970	5.025	1.266	9	***
***GM	5.093	3.394	0.2917	5.168	0.7717	16	***
***GM	6.248	2.907	0.2905	5.122	0.5632	23	***
***GM	6.448	2.684	0.2898	4.188	0.4999	30	***
***GM	6.685	2.339	0.2842	3.262	0.4431	39	***
***GM	6.829	2.099	0.2768	3.186	0.3668	47	***
***GM	6.979	2.158	0.2768	3.178	0.3572	55	***
***GM	7.266	1.988	0.2764	3.096	0.3521	64	***
***GM	7.271	1.991	0.2766	3.130	0.3518	73	***
***GM	7.272	1.990	0.2766	3.129	0.3518	80	***
**LOC	7.277	1.990	0.2766	3.129	0.3518	111	***
***GM	7.277	1.990	0.2767	3.129	0.3518	130	***
***GM	7.277	1.991	0.2767	3.129	0.3518	141	***
**LOC	7.283	1.991	0.2767	3.129	0.3518	167	***

PTIMUM PARAMETERS :-

7.28	1.99	0.277	3.13	0.352

PT0 = 43.57

TIME TAKEN = 00:06:25

NUMBER OF ITERATIONS = 200

NOLLS

TABLE 6.4

DATA FILE : RP0142

VD = 0.146 HB = 15.00 SB = 0.00434 PAIN = 37.951 PABAR = 37.786 MP = 0.26020

THRES = 0.100000E-02 STEP = 1.000 SIGMA = 0.900

	QDOT	VA	MP	VT	F(ERR)	ITER	
***LS	5.000	5.000	0.2000	5.000	15.17	1	***
***LS	5.960	3.514	0.2372	1.984	4.902	3	***
***LS	7.849	1.873	0.2737	3.064	0.3896	4	***
***LS	7.303	1.965	0.2765	3.109	0.3520	5	***
***LS	7.290	1.986	0.2766	3.127	0.3518	7	***

OPTIMUM PARAMETERS:-

7.29016 1.98629 0.276645 3.12677 0.351817

PTOSS = 43.56 NO OF OBSERVATIONS = 60

NO OF ITERATIONS = 11

TIME TAKEN = 00:02:02

COMPARISON OF CONVERGENCE OF 'GMOPT' AND 'NOLLS' FOR FOUR PARAMETER MINIMISATION OF FILE RP0142·PRO.

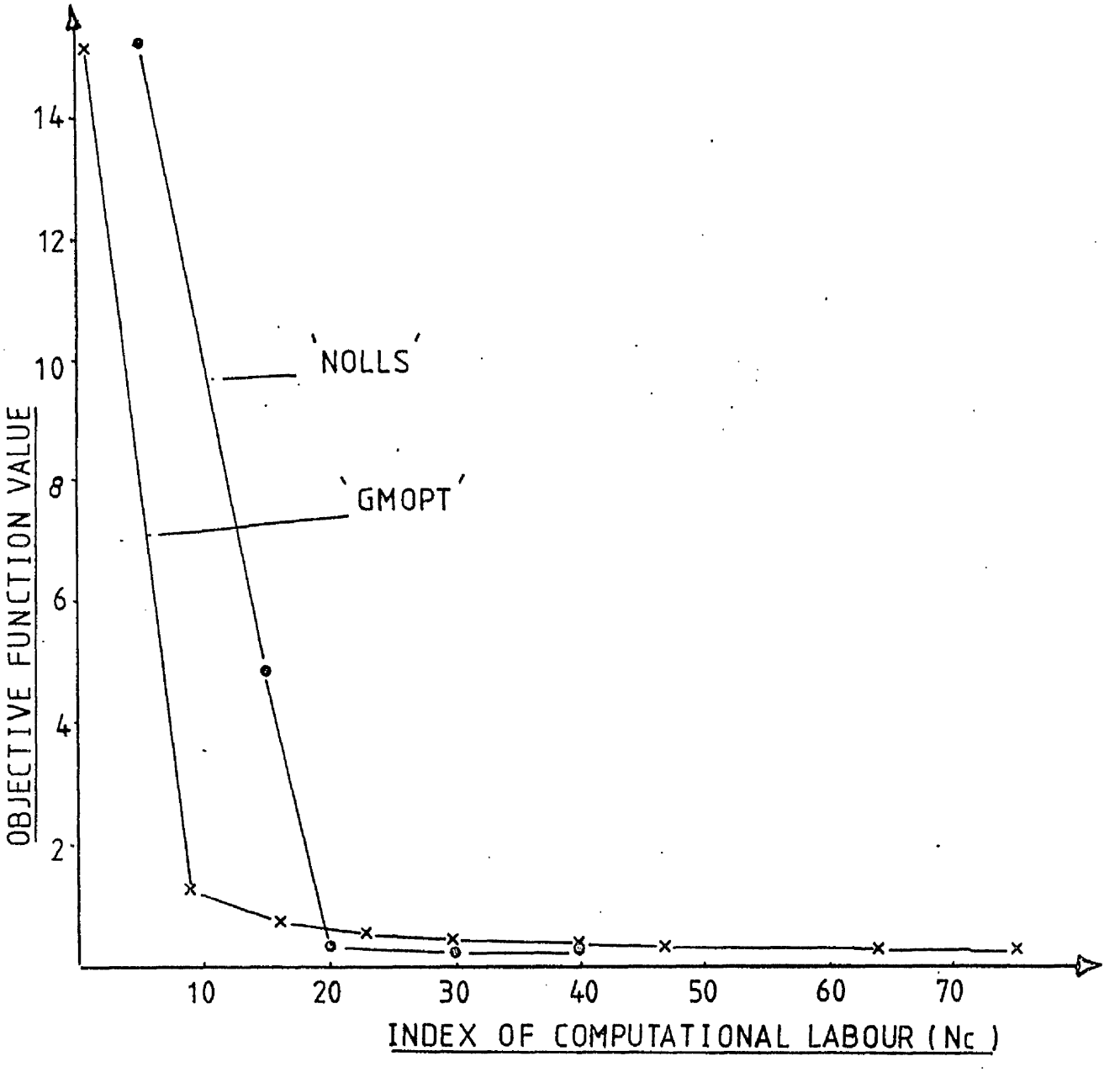


FIGURE 6·1

$$e = L\varepsilon \qquad 6.32$$

where $$e = y_M - y_D \qquad 6.33$$

L is proportional to the 'square-root' of the covariance matrix of the errors, i.e.

$$\text{cov.}(e) = N = \sigma^2 L L^T \qquad 6.34$$

and ε is an assumed set of Gaussian i i d random variables.

In Chapter 4 it was shown that maximising the likelihood function $L(\beta)$ required knowledge of the elements of N. These are generally unknown a priori and hence must be estimated. However, due to the large number of parameters in N (which is an $m \times m$ matrix where m is the number of observations) the resultant minimisation problem becomes untenable in the general case.

By assuming a certain form of 'noise model' however (i.e. first order auto-reggressive process) N is dependent on only two parameters (a,b) and is of a form which is extremely convenient for computational purposes. Under these conditions maximising $L(\beta, N)$ is equivalent to minimising

$$V(\beta, a, b) = \sum_{i=1}^{m} \varepsilon_i^2 = \varepsilon^T \varepsilon \qquad 6.35$$

which is in a sums of squares form.

Thus, rather than minimise $\sum e_i^2$ as in the ordinary least squares case, we minimise $\sum \varepsilon_i^2$ where from equation 6.32

$$\varepsilon = L^{-1} e \qquad 6.36$$

Due to the particular structure of L and L^{-1} in the first order ARMA process case the residuals ε can be calculated recursively from the

deterministic errors e

$$\varepsilon_i = e_i - a\, e_{i-1} - b\, \varepsilon_{i-1} \qquad 6.37$$

which thus avoids calculation and storage of L^{-1} . The deterministic errors can be recovered from the residuals similarly by the inverse relationship. The sensitivity matrix Z can also be calculated in a recursive manner. It is given by

$$Z = \left[Z_1 \,\vdots\, Z_2 \right] \qquad 6.38$$

Z_1 being the sub-matrix of sensitivities of ε with respect to the determinstic model parameters and Z_2 the sensitivities with respect to the 'noise' parameters a and b . A typical term in Z_1 can be calculated recursively from the model sensitivities in the ordinary least squares case, e.g.

$$Z_1\ i, j = \frac{\partial y_{Mi}}{\partial \beta_j} - a \frac{\partial y_{Mi-1}}{\partial \beta_j} - b\ Z_1\ i-1, j \qquad 6.39$$

From equation 6.37 the sensitivities of the two noise model parameters are:

$$\frac{\partial \varepsilon_i}{\partial a} = -e_{i-1}\ ,\ \left(\frac{\partial \varepsilon_1}{\partial a} = 0 \right) \qquad 6.40$$

$$\frac{\partial \varepsilon_i}{\partial b} = \varepsilon_{i-1}\ ,\ \left(\frac{\partial \varepsilon_1}{\partial b} = 0 \right) \qquad 6.41$$

These make up the matrix Z_2 .

Thus from the above it is apparent that although the number of parameters in the minimisation problem is increased from a maximum of six in the ordinary least squares case to eight in the 'MAXL' case, the resultant

increase in computational labour will not be proportionately as great. This is because it is not necessary to solve additional co-systems of differential equations to calculate the noise sensitivities since calculating them involves only trivial analytic manipulation of already known quantities.

CHAPTER 7

IMPROVED EXPERIMENTAL DESIGN AND NEW RESULTS FOR THE NON-INVASIVE CARDIAC OUTPUT MEASUREMENT METHOD.

7.1 Introduction

In Chapter 4 of this thesis the estimates obtained from the homogeneous CO_2 identification procedure were analysed. From this analysis the conclusion was reached that, although the cardiac output estimates obtained from these validation experiments were competitive with any similar technique that has hitherto appeared in the literature (e.g. see Homer and Denysk (155)), the form of test signal used (40 sec air followed by 7/5% CO_2) did not excite the system sufficiently for identification purposes. In retrospect, this poor nature of the test signal is hardly surprising since most of the interest in the work had until then centred on the data analysis. The informational aspect of the problem has hitherto been largely ignored except a posteriori (see Chapter 4).

Astrom and Bohlin (11) and Aoki and Staley (5) defined the condition of 'persistent excitation' as being a necessary one for a test signal to possess in order to produce consistent estimates. Conceptually all this means is that the band width of the signal is such that it allows all the modes of the system under test to be perturbed. Practically, however, it has been well known for some time (187, 182, 216) that the choice of test signal has a significant bearing on the results of an identification. This was first noticed in the system identification field by Levin (184) in 1960 when he considered the estimation of the impulse response of a discrete time linear single input single output model corrupted by additive white measurement noise.

It has been shown that the use of optimal test signals allows the achievable accuracy to be greatly increased as compared to arbitrary inputs such as e.g. pseudo-random -binary sequences (PRBS) (43) which are widely used in the identification literature. This is because the optimal test signals

allow the maximum amount of information to be extracted from the system under scrutiny. This chapter describes the design of such test signals in connection with estimating the parameters of the homogeneous CO_2 model. The aim in this is to use these signals to produce a much more reproducible non-invasive caradiac output estimation scheme. Also presented in this chapter is a theoretical investigation carried out to determine the type of model (e.g. CO_2 , O_2, inert gas, etc.) which allows cardiac output to be best estimated. This analysis was felt to be an essential preliminary to the optimal test signal design for a given model. First, however, a brief literature review is presented on optimal design and some theory necessary for the work detailed later in the chapter is developed.

7.2 Brief Review of Optimal Experiment Design

Optimal test signal design can be viewed as a sub-problem of the wider problem of experiment design. In the static case (e.g. as applied to design of linear and non-linear regression experiments) this problem has been of great interest to statisticians for many years (39, 104). Only comparatively recently has this mutual interest been exploited and any significant cross-fertilisation taken place between the engineers and statisticians (206).

In the dynamic system identification literature the experiment design problem has been approached in a number of different ways. In the time domain synthesis, given that a scalar function which is a measure of the optimality of an experiment has been defined, the problem essentially reduces to what is a two-point boundary value problem. This is equivalent to the standard non-linear optimal control problem which is discussed in many texts on modern control theory (95). An advantage of this approach is that it is easily extended to take account of typical constraints which it may be necessary to impose on the experiment in a real-life situation, e.g. amplitude or power constraints on input, constraint on total experiment time, maximum sampling rate, etc. This problem can, in principle, be solved by the usual dynamic optimisation procedures (270). The time domain optimal control approach has been used and refined in many ways by Goodwin and his collaborators (133, 134, 135, 138) and Mehra (205, 206). In (135) Goodwin, Murdoch and Payne discuss optimal test signal design for the often used single-input single-output (SISO) transfer function model of Astrom and Bohlin (11) discussed in Chapter 1. In (134) Goodwin, Zarrop and Payne consider the wider problem of coupled design of test signal, sampling interval

and pre-sampling filter.

The optimal experiment problem has also been investigated in the frequency domain. A procedure to compute the optimal input auto-correlation function was developed by Goodwin and Payne (136). At about the same time, Van Der Bos (285) gave a method for realising specified A.C.F's. recursively using a binary signal. These two procedures may thus be combined to form a useful alternative to the time-domain optimal control approach discussed above.

Mehra (205) proves the useful result that in the frequency domain, the optimal test signal can be found to consist of a weighted sum of a finite number of sinusoids. The significance of this result is that what is an infinite dimensional problem in the time domain is reduced to only a finite dimensional problem in the frequency domain and is consequently easier to solve. This result is exploited in (219, 233) where the optimal sampling strategy for system identification is considered in the frequency domain.

The approches discussed so far both in the time and frequency domain have been statistical in origin, i.e. the criteria of optimality used have been developed from statistical considerations. Many authors have adopted a more deterministic approach to the problem. Rault and his co-workers emphasise the connection between sensitivity and the accuracy of the estimates and discuss test signal design criteria based on sensitivity considerations in both the time domain (242) and frequency domain (239). In (241) Rault notes that many of these heuristic criteria can be given statistical interpretations. Inoue et al (161) report further work based on the sensitivity approach.

To avoid the complexity inherent in the full time domain optimal

control approach Keviczky and Banyasz (174) outline a simpler sequential approach potentially useful for on-line identification situations. This method has also been derived on information theoretic grounds by Arimoto and Kimura (6). They show that the procedure is optimal in a one step ahead sense (i.e. it maximises the incremental increase in information during the next measurement period). Note however that this does not imply global optimality (i.e. optimality over the whole experiment period) since the algorithm takes no account of future learning.

To date few practical applications of the otpimal experiment design techniques have been reported in the engineering literature. Perhaps this is due in no small measure to the mathematical complexity of the techniques. Among those which have are Goodwin ((134) - application to identification of a steam generator) and Mehra ((205) - application to identification of the parameters of aircraft dynamics).

In the biomedical field applications are almost non-existent. This is despite the obvious usefulness of these methods in an area where identification rather than identification and control is usually the main objective. A noteable exception in this respect is the work of Swanson (272, 273). Swanson devotes almost all of Chapter 5 of his thesis (272) (which is concerned with investigation of the respiratory control system as mentioned earlier) to the optimal test signal design problem.

Finally, in concluding this short review section, it is appropriate to draw attention to the following two references as having made a significant contribution to the field. Mehra (206) reviewed the state of the art in optimal experiment design for system identification in the special issue of I.E.E.E. Transactions on Automatic Control dedicated to System Identification in December 1974. Also, Chapter 6 of the recent book by Goodwin and Payne (31) gives an excellent treatment of the experiment design problem.

7.3 Criteria of Optimality

The use of optimal experiment design techniques presupposes that some quantifiable measure of the goodness of an experiment is available. In the previous section, this measure has been intuitively tied up with notions related to, on the one hand, some concept of maximising the information content of the data, and on the other maximising the expected precision of the estimates. In fact, it transpires identical optimal experiment design criteria can be derived utilising either approach. However, the statistical approach is most commonly adopted.

A measure of the precision of a parameter estimate is of course its variance. This is a function of both the experiment design and the type of estimation technique used. In the optimal experiment design literature it is customary to assume the estimator used is efficient, so that the Cramer-Rao Lower Bound is achieved. This is sensible since the optimal experiment design can be synthesised independently of the estimator resulting in greater simplicity.

Thus, this approach leads to defining measures of goodness based on the Fisher Information Matrix $\underline{M}$ of the following form

$$J = f(\underline{M}) \qquad 7.1$$

f denoting an appropriately chosen function of $\underline{M}$ which is necessarily scalar.

Recall from Chapter 4 that for a model non-linear in the parmeters, such as is considered in much of this thesis, $\underline{M}$ will be dependent on the actual numerical values of the parameters. These, of course, will not be known a priori. In practice, therefore, the information matrix $\underline{M}$ is usually evaluated at a representative set of parameter values e.g. an earlier estimate

if this exists. Thus, it is advisable to check the sensitivity of the design to this parameter choice once it has been found. One design criterion frequently used in the literature (135, 138, 205) is the following :-

$$\min J = \text{trace} (\underline{W}\ \underline{M}^{-1}) \qquad 7.2$$

where $\underline{W}$ is an arbitrarily chosen weighting matrix to account for the parameters having differing magnitudes, etc. This criterion can be thought of as minimising the weighted mean of the variance of the estimates. With W = I this criterion is identical to Federov's (104) A-optimal criterion discussed in the literature. Goodwin and Payne (137) argue that equation 7.2 is the natural criterion to adopt from Bayesian considerations. If one considers a design criterion as being chosen as a risk function reflecting the estimated models intended use then Goodwin and Payne put forward heuristic arguments to show that minimising equation 7.2 is equivalent to optimising this Risk function with W chosen suitably.

Some authors (5, 184) have advocated use of the following type of criterion,

$$\max J = \text{trace} (\underline{W}\ \underline{M}) \qquad 7.3$$

Use of this criterion reduces the complexity of the design procedure since it allows linear quadratic theory to be used to solve the resultant optimal control problem. However, this has been criticised by Goodwin and Payne (136) who show that the use of the above criterion can lead to the choice of experiments for which M is singular. Thus, the parameters will be unidentifiable which is clearly undesirable. The optimal experiment design criterion which is most often used is the so-called D-optimal (104) criterion.

$$\min J_D = \det (M^{-1}) \qquad 7.4$$

The idea for this criterion was first proposed in the statistical literature by Box and Lucas (40) in 1959. This criterion can be interpreted as that which minimises the volume of highest probability density region for the parameters. Another interesting aspect of this criterion is that unlike previous criteria mentioned, it is invariant under scaling of the parameters. This criterion will be the one on which the work in the rest of this Chapter is based.

Beck and Arnold (22) show the above criterion can be derived independently via information theory, utilising Shannon's concept of a measure of uncertainty (257). The same parallel is drawn elsewhere (137, 66).

The D-optimal criterion results in a test signal which implicitly attempts to distribute information equally on all the parameters. Suppose, however, we are interested in estimating accurately only a subset of these parameters (the first i say). The rest of the parameters perhaps, although necessary for the estimation, are really superfluous as far as the investigator is concerned. (Note this corresponds exactly to be situation with which we are dealing in the non-invasive cardiac output determination.) Under these conditions the experiments must satisfy different criteria related only to the accuracy of those parameters of interest. Hunter, Hill and Henson (159) thus advocate the following criterion.

$$\min J_{D_t} \det \left(M_{ii}^{-1} \right) \qquad 7.5$$

where M_{ii} is a submatrix of the full information matrix M which refers to the i parameters of interest. Federov (104) has called this a truncated D-optimal design (D_t). Having introduced the D-optimal criterion we will now derive what this reduces to for the case of the two different types of estimation error structure considered in Chapter 4. That is the ordinary

least squares (OLS) and auto-regressive moving average (ARMA) noise models.

Recall from Chapter 4 that in the OLS case

$$M = \hat{\sigma}^2 \left[X^T X \right] \qquad 7.6$$

and the D-optimal criterion thus is

$$\min J_D = \det \left\{ \left[X^T X \right]^{-1} \right\} \qquad 7.7$$

X being the parameter sensitivity matrix, as in Chapter 4.

Suppose only 'i' of the 'n' parameters need be estimated accurately. If the sensitivity matrix X is partitioned as

$$X = \left[X_1 X_2 \right] \qquad 7.8$$

where X_1 refers to the 'i' parameters of interest, then the truncated D-optimal criterion can be written as

$$\min J_{D_t} = \det \left\{ \left[X_1^T X_1 - X_1^T X_2 (X_2^T X_2)^{-1} X_2^T X_1 \right]^{-1} \right\} \qquad 7.9$$

The information matrix which results from the use of the ARMA noise model is of the following special form (135)

$$M = \left[\begin{array}{c|c} M_1 & O \\ \hline O & M_2 \end{array} \right] \qquad 7.10$$

where M_1 is the information matrix of the deterministic model parameters and M_2 that of the noise model parameters. M_1 is independent of the error as M_2 is independent of the test signal (135). Thus, in this situation optimal designs can only be synthesised to estimate the determinstic model parameters. This is done by replacing X in the criterion functions defined by equations 7.7 and 7.9 by the modified sensitivity matrix Z_1 for the determinstic model

parameters in the ARMA noise case (see equations 6.38 and 6.39).

7.4 Optimal Experiment Design for the Homogeneous CO_2 Model

We will now describe investigations carried out to determine the most suitable form of test signal for estimation of the parameters of the homogeneous CO_2 model utilising the concepts outlined in the previous sections of this chapter.

It is intuitively obvious that to obtain the most accurate estimates of the parameters we should like our test signal amplitude and our observation time as large as possible, i.e. the optimal test signal design criteria mentioned in the previous section (equations 7.7 and 7.9) can be driven to zero by allowing both of these quantities to approach infinity. However, in this application, as in many other biomedical applications, physiological and ethical factors impose severe constraints on the choice of test stimulus that can be applied. For example, a frequent worry is that the input disturbances may influence parameters and system variables through feedback mechanisms. In the respiratory system, ventilation is the main controlled quantity, as mentioned in Chapter 2. However, in our application although ventilation is a component in our model, it is measured and treated as a known input disturbance. Thus, any change in ventilation due to feedback from chemoreceptors or pulmonary receptors can have no effect on the estimation. Note that since ventilation is also under autonomous control, in theory this raises the question of using this as an additional manipulatable input to the model. This was ruled out because of the desire to retain the advantage the current form of procedure possesses over routine pulmonary function tests. That is, of being able to free the untrained subject from the neccesity to perform complicated ventilatory

manouevres. This aspect of the procedure was felt by the clinicians to be of great benefit in a routine situation and far outweighs any advantages which might accrue from including ventilation as a manipulatable variable in the experimental design.

It is also important to check that the choice of test signal induces no variations in the parameters over the course of the experiment. The effect of breathing CO_2 on cardiac output has in fact been documented (110, 204b). On the basis of (110), Pack (228) concluded that the form and duration of the experiment used in the validation studies (7/5% CO_2 for 2 mins) produces no significant changes in the homogeneous CO_2 model parameters due to physiological control mechanisms. However, it has been impossible to check the effects of these assumptions statistically since unidentifiability problems were encountered when it was attempted to estimate models over only partial lengths of the validation data (e.g. the air breathing part). This is hardly surprising given the conclusions of Chapter 4. There is nothing, however, in the results presented in Chapter 4 to lead one to discount the assumption of stationarity of the estimates. For longer forms of experiment the implications are less clear. Fishman et al (110) reported no change could be detected in cardiac output in normal subjects after 15 to 20 minutes breathing either 5% or 7% CO_2 . McGregor et al (204b) reported changes in cardiac output following 8.4% CO_2 inhalation after 2 minutes. However, checking stationarity à posteriori should present no problems in this situation. Thus it was decided to adopt an empirical approach to the design problem in this respect. That is in the first instance in the design study it was decided to limit the maximum concentration of CO_2 to 7% and maximum experiment duration to 10 minutes. The latter time was chosen since it was

felt to be the maximum time for which it was felt a subject could reasonably tolerate CO_2 breathing without any great discomfort. However, it was recognised that this experiment duration might have to be reduced if the resultant estimates were found to be non-stationary or the experimental procedure was in fact found to be too arduous. As it transpired, both these reservations proved to be unnecessary. In preliminary experiments occasionally some subjects when breathing 7% CO_2 elicited too great a ventilation response and subsequently became uncomfortable due to the increased work in breathing through a mouthpiece. However, with these subjects the CO_2 concentration was reduced to 5% which they found perfectly acceptable. Thus, having constrained the prospective inspired PCO_2 test stimuli in both amplitude and duration the problem reduces to find the optimal time course of the signal waveform within these boundaries. It would, therefore, seem possible to directly apply the elegant time-domain optimal control techniques in this situation. This was in fact the original intention. At this stage, however, considerations arose which seemed to indicate this just might not be entirely appropriate. These were as follows.

The first concerns the cyclic nature of ventilation. Although the optimal control type techniques can be applied directly to the 'flow through' model (see Chapter 2), for the cyclic model the input is not really defined during expiration. Thus, the state of the input can only really change at time instants during the inspiratory period. This may not coincide with times dictated by the optimal sequence. Thus a 'breath by breath' approach is needed. The second consideration is more practical and again inevitably is tied up with the ultimate applicability of the technique. Although it is conceivable that ultimately the CO_2 test signal will be computer generated, it is far more likely,

that in the foreseeable future it will be done, as at present, by manual switching of a valve. In a routine situation this is likely to be done by a physiological measurement technician. It is, therefore, desirable that the test signals should be simple to administer, e.g. square waves rather than complicated binary sequences.

In view of the above it was decided that use of the full optimal control approach was practically unjustifiable. A more limited approach was, therefore, adopted and a square wave design sought, i.e. the best on/off switching frequency which minimises the criteria discussed in the previous section.

For this a general homogeneous CO_2 gas transport simulation programme (LUNG 1) was written to allow the various criteria of optimality of an experiment to be evaluated for a given set of model parameters and experimental conditions. The sensitivity coefficients necessary to calculate the criteria were obtained from the model using finite differences. A sinusoidal breathing pattern was assumed in the absence of any other a priori information. Although Etsyon et al (97a) have proposed a more complicated ventilation profile, the sinusoidal approximation is felt to be adequate for our purposes and also has the advantage of being more convenient mathematically.

The amplitude of the sinusoidal breathing pattern can be tailored to achieve approximately the desired average alveolar minute ventilation using the following equation :

$$V_{max} = \pi (\dot{V}_A + f V_D) \qquad 7.11$$

The simulation programme is quite general in that it allows other test signals e.g. steps and general binary sequences to be investigated in addition to square waves.

The model conditions chosen as the basis of the square wave experiment design investigations are detailed in Table 7.1. The total number of breaths in the experiment was set at 150. Using LUNG 1 (and assuming for the moment a six parameter model) a measure of the information content of the experiment was calculated (i.e. a measure corresponding to the inverse of equation 7.7 or 7.9) for various (integer) values of square wave input period (in breaths). This was first assuming (a) all the parameters were of equal importance (J_1) and then (b) only cardiac output ($\dot{Q}$) was of importance. The results are plotted in Figure 7.1.

These results are interesting in that they indicate that extrema of the two design criteria do in fact exist over the range of input switching periods studied. It is also apparent that the best design for distributing information on all the parameters does not coincide with the best design for the case where cardiac output is the only paramater of importance : in the former case the appropriate switching period is 60 breaths (i.e. $\approx$ 4 mins) whilst in the latter case it is 24 breaths ($1\frac{1}{2}$ minutes). In the case of a four parameter CO_2 model the results were found to be quantitively similar.

To investigate the sensitivity of the design to parametric and ventilatory variations, a modified version of the linear search procedure discussed in Chapter 5 and Appendix B was incorporated into the LUNG 1 programme. This allowed the procedure of determining the best switching frequency to be automated. From subsequent analysis it transpired, surprisingly, that the design was quite robust. Over the range of model and ventilatory parameters encountered in resting conditions (c.f. the validation data), the best switching period for cardiac output estimation was

Table 7.1 : Prior Parameter Values Chosen As A Basis for Optimal Test Signal Design Investigations

(i) determinstic model parameters

$\dot{Q}$	-	5 litres / min
$V_A(0)$	-	5 litres
$\dot{M}$	-	0.2 litres / min
V_{TC}	-	5 litres
$P_A(0)$	-	Steady state value
$P_{TC}(0)$	-	Steady state value (see equation 3.13)

(ii) noise model parameters (where applicable)

a	-	- 0.8
b	-	- 0.05

(iii) constants

Hb	-	16.0 gm %
A_{INT}	-	0.0129
$\dot{V}_A$	-	6 litres / min
V_D	-	0.2 litres
f	-	15 breaths / min.

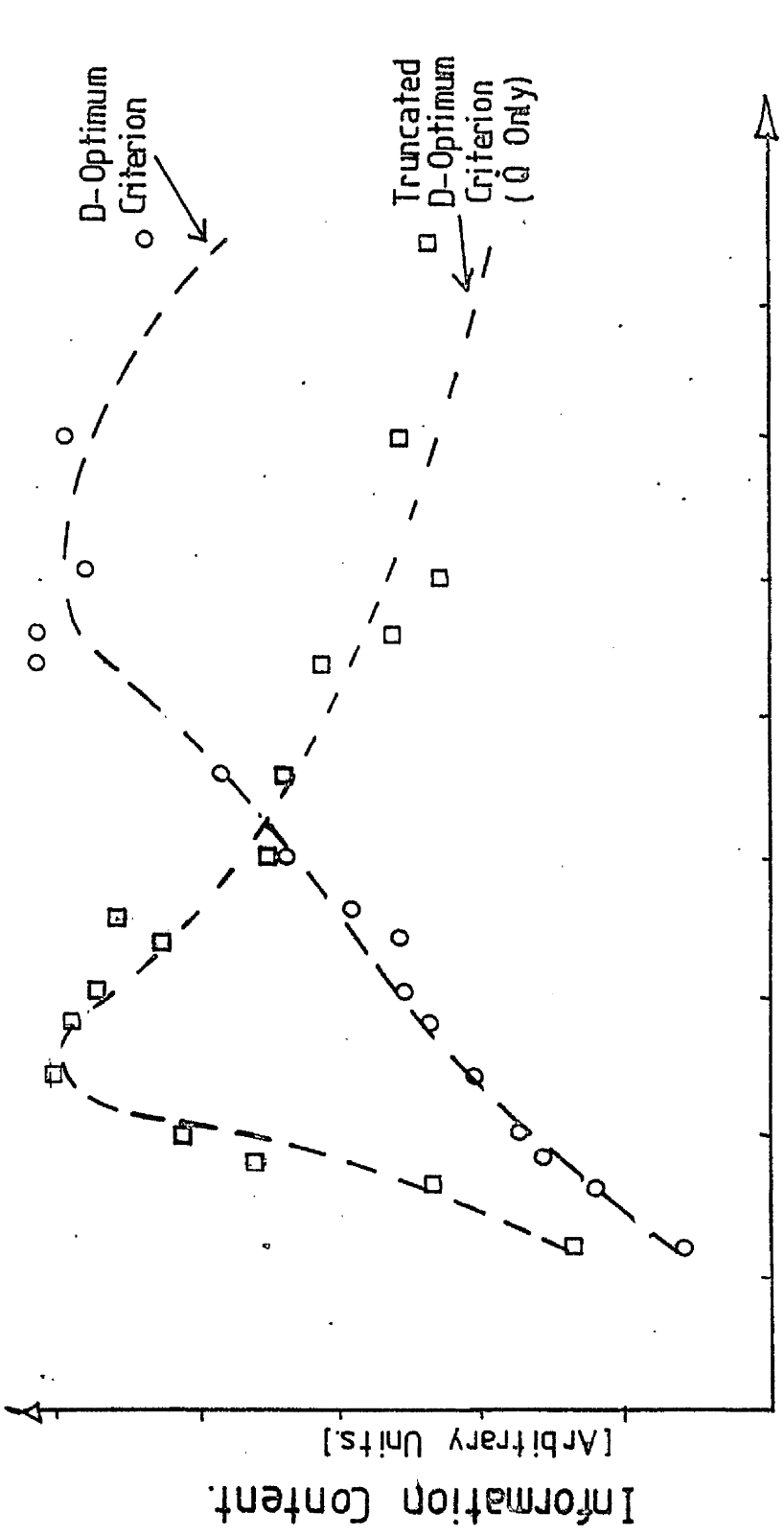

TEST SIGNAL OPTIMALITY CRITERIA Vs CO2 SWITCHING PERIOD ASSUMING LEAST SQUARES NOISE MODEL
D-Optimum Criterion
Truncated D-Optimum Criterion (Q Only)
Information Content
[Arbitrary Units]
10
20
30
40
50
60
70
80
Square Wave Period.
[Breaths]

FIGURE 7.1

roughly in the range 70 - 150 seconds. However, it may be necessary to reassess this design for exercise studies.

The optimal designs for $\dot{Q}$, V_A, $\dot{M}$ and V_{TC} (assuming each parameter in turn is the main one of importance) are plotted in Figure 7.2. The measures of information content for the initial conditions $P_{A(0)}$ and $P_{TC(0)}$ were found to be frequency invariant, as one would intuitively expect, and are therefore not shown in Figure 7.2.

From Figure 7.2 it is apparent that a fast switching test signal (high frequency) is appropriate for optimal estimation of lung volume V_A, whilst a longer switching period is best for estimating $\dot{M}$ and V_{TC}. This again is as expected since V_A is associated with the faster alveolar time constant whilst $\dot{M}$ and V_{TC} are associated with the slower tissue dynamics. In this respect, the best switching period for $\dot{Q}$ (which relates to the transfer between the two compartments) can be thought of as a compromise.

In Table 7.2 the best square wave input (period 24 breaths) results are compared with those obtained using less enlightened inputs. That is a step ON at 1 min for 9 minutes and a 127 bit pseudo-random binary sequence with a clock rate equal to one breath.

This latter form of test signal might perhaps have been chosen to use in the first instance without attempting to take too much account of a priori structure. Implicitly this test signal attempts to evenly distribute the input power over a broad frequency spectrum. This is a good general strategy. However, if specific structural knowledge of the model is possessed a better approach is to take advantage of this to design inputs which concentrate the power at the frequencies important for that particular model. That this is good sense is clearly illustrated in the results of Table 7.2.

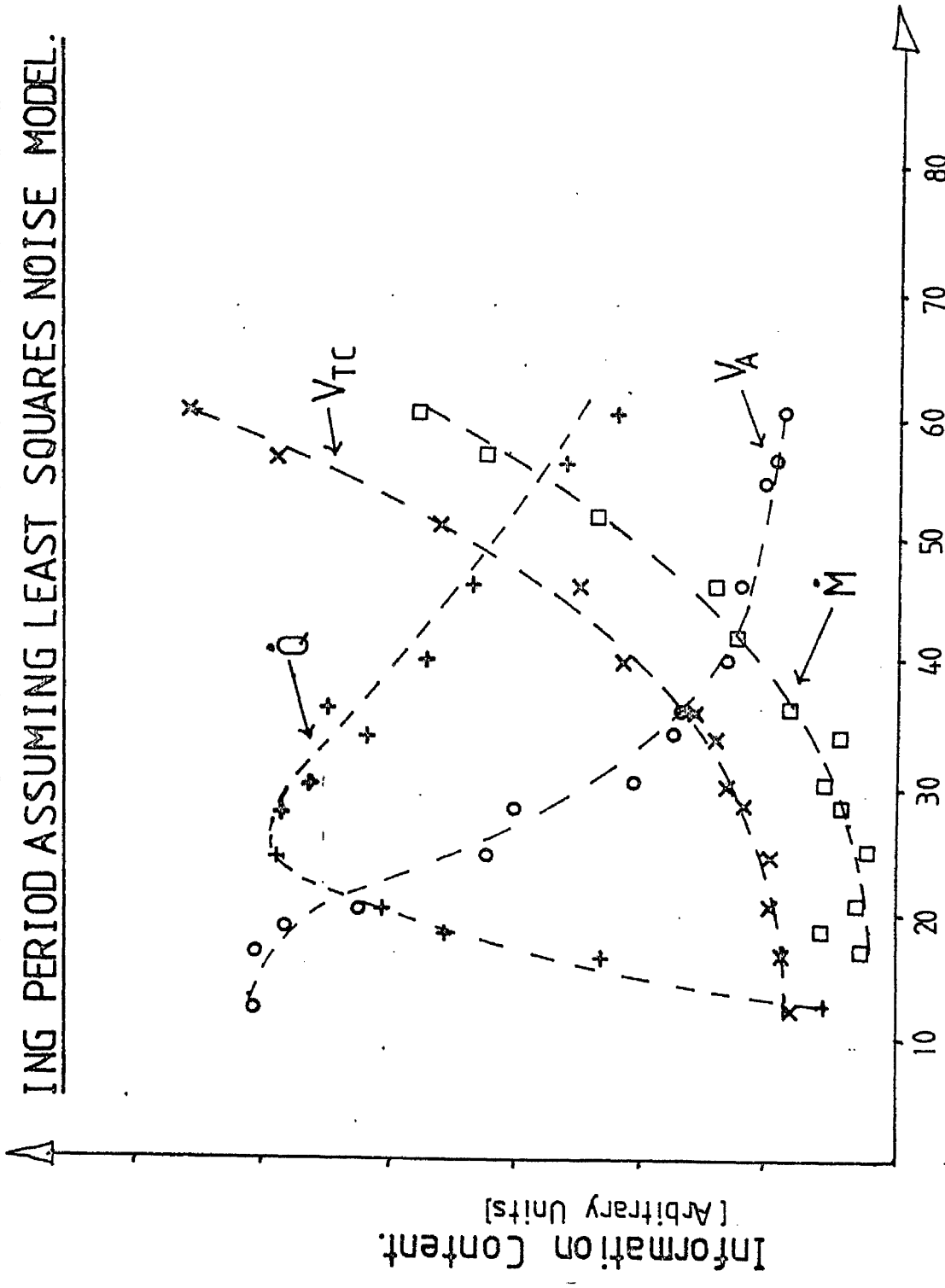

SINGLE PARAMETER OPTIMALITY CRITERIA Vs CO2 SWITCH-
ING PERIOD ASSUMING LEAST SQUARES NOISE MODEL.
Information Content.
[Arbitrary Units]
Square Wave Period
[Breaths]
10
20
30
40
50
60
70
80
$\dot{Q}$
V_{TC}
V_A
$\dot{M}$

FIGURE 7.2

Table 7.2

Comparison of Optimality of Different Input Signals

Input	Information Measure ($\dot{Q}$ only of importance)	Information Measure (All model parameters of importance)
STEP ON at 1 min for 9 mins	160.78	4.15×10^{18}
OPTIMAL SQ WAVE (period 24 breaths)	699.30	40.98×10^{18}
127 BIT PRBS (Cycle time 1 sample)	192.68	10.53×10^{18}

Plots of the sensitivity functions for the step input and the square wave input are given in Figures 7.3 and 7.4 respectively. These show that for the step input the model is only sensitive to $\dot{Q}$ and V_A over a small part of the total experiment, i.e. this form of input is not "persistently exciting". On the other hand, for the square wave input the model exhibits distinct sensitivity to all the parameters throughout the whole experiment.

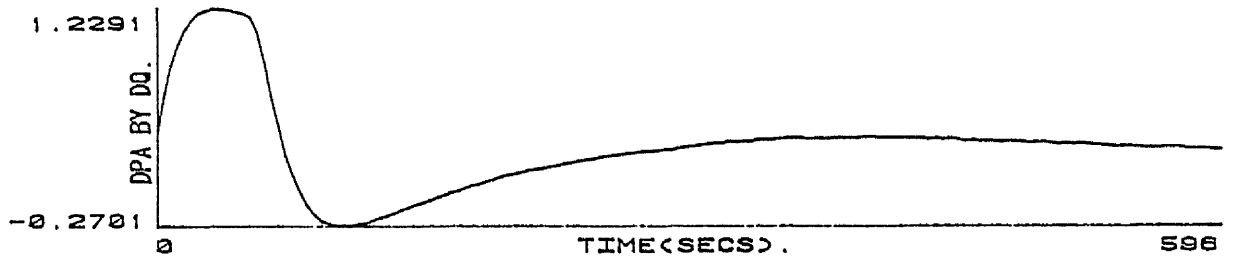
Earlier experiment design results also illustrate very well the folly of basing truncated experiment design criteria on the diagonal elements of the information matrix rather than its inverse. (This corresponds to using criteria of the form of equation 7.3.) For example, consider the following criterion based on maximising the diagonal element of the information matrix which is equivalent to the following:

$$\max J = \sum_{i=1}^{M} \left(\frac{\partial Y_{M_i}}{\partial \dot{Q}} \right)^2 \qquad 7.12$$

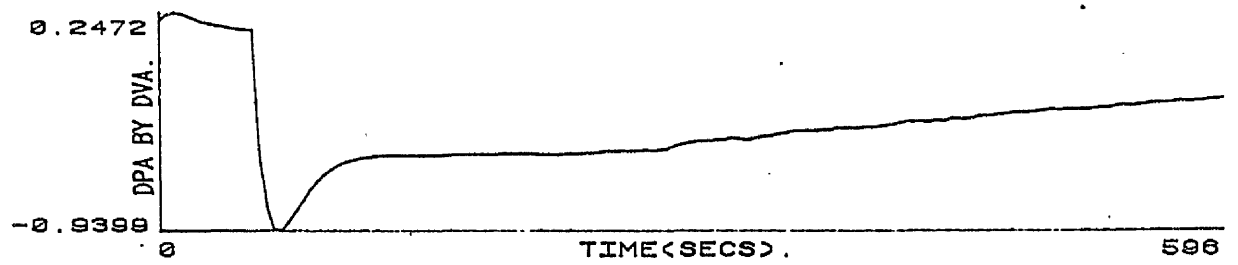
Y_{Mi} being the flow weighted mean of the model output at the i^{th} breath. On the surface this appears, in fact, a reasonable criterion to use to design a good experiment for cardiac output estimation. However, this criterion does not properly account for interactions among the parameters. This can be seen from the results in Table 7.3 where the value of criterion is seen to be maximised for long switching periods.

Finally, the best design assuming an ARMA noise structure was studied for the model conditions discussed earlier. The results are plotted in Figure 7.5. These again show the best design is not greatly different from that obtained in the least squares case.

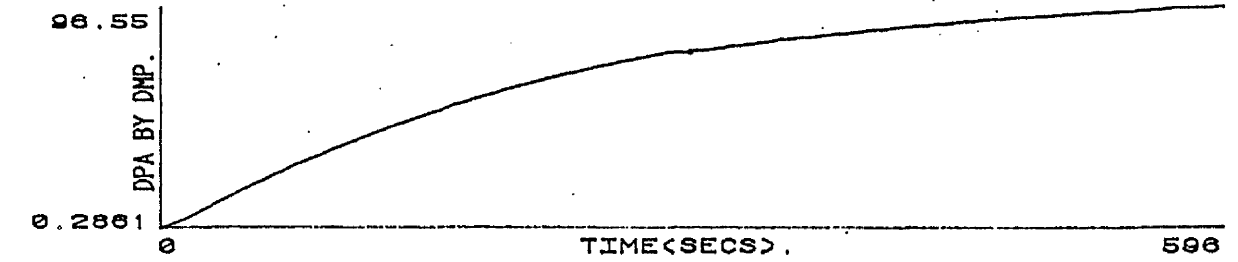
CO2 MODEL-SENSITIVITY FNS FOR STEP INPUT.



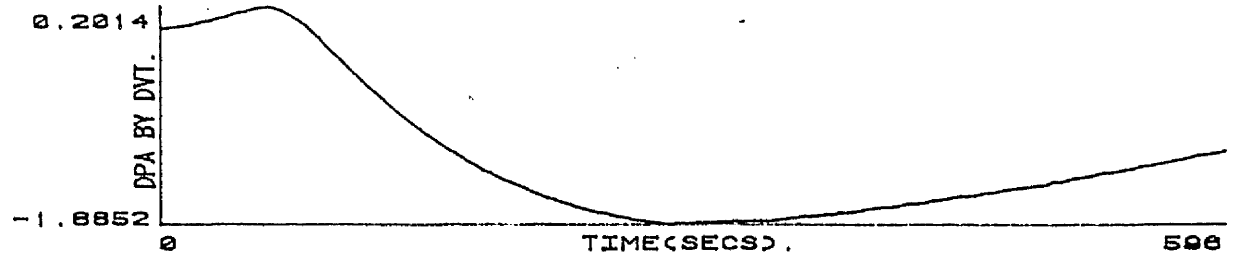
SENSITIVITY TO CARDIAC OUTPUT.



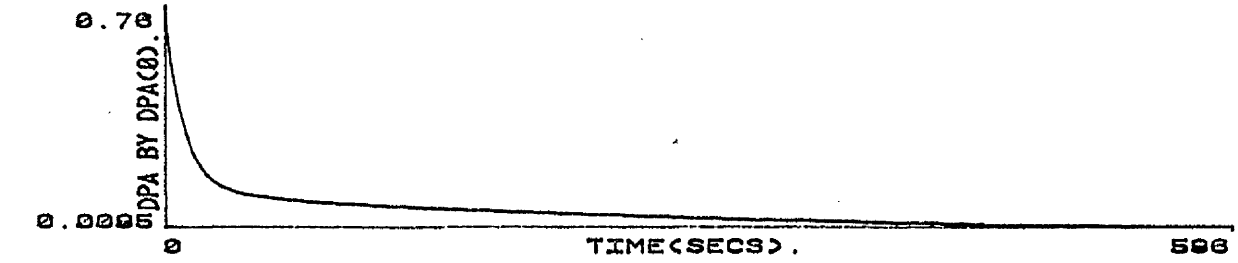
SENSITIVITY TO LUNG VOLUME.



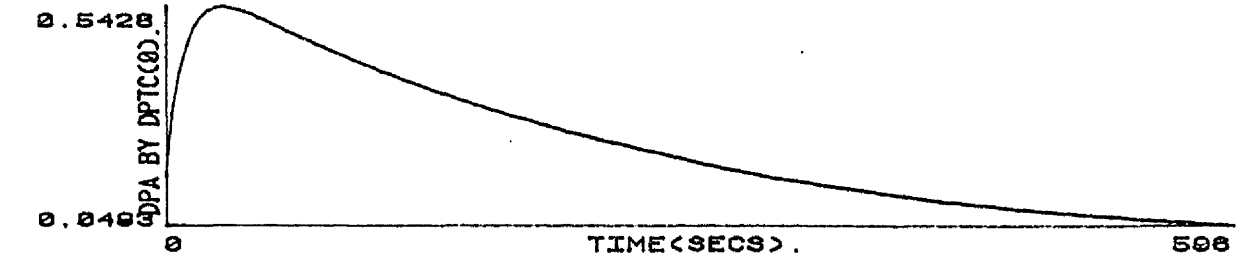
SENSITIVITY TO METABOLIC PRODN.



SENSITIVITY TO TISSUE VOLUME.



SENSITIVITY TO INITIAL LUNG PCO2.



SENSITIVITY TO INITIAL TISSUE PCO2.

FIGURE 7·3

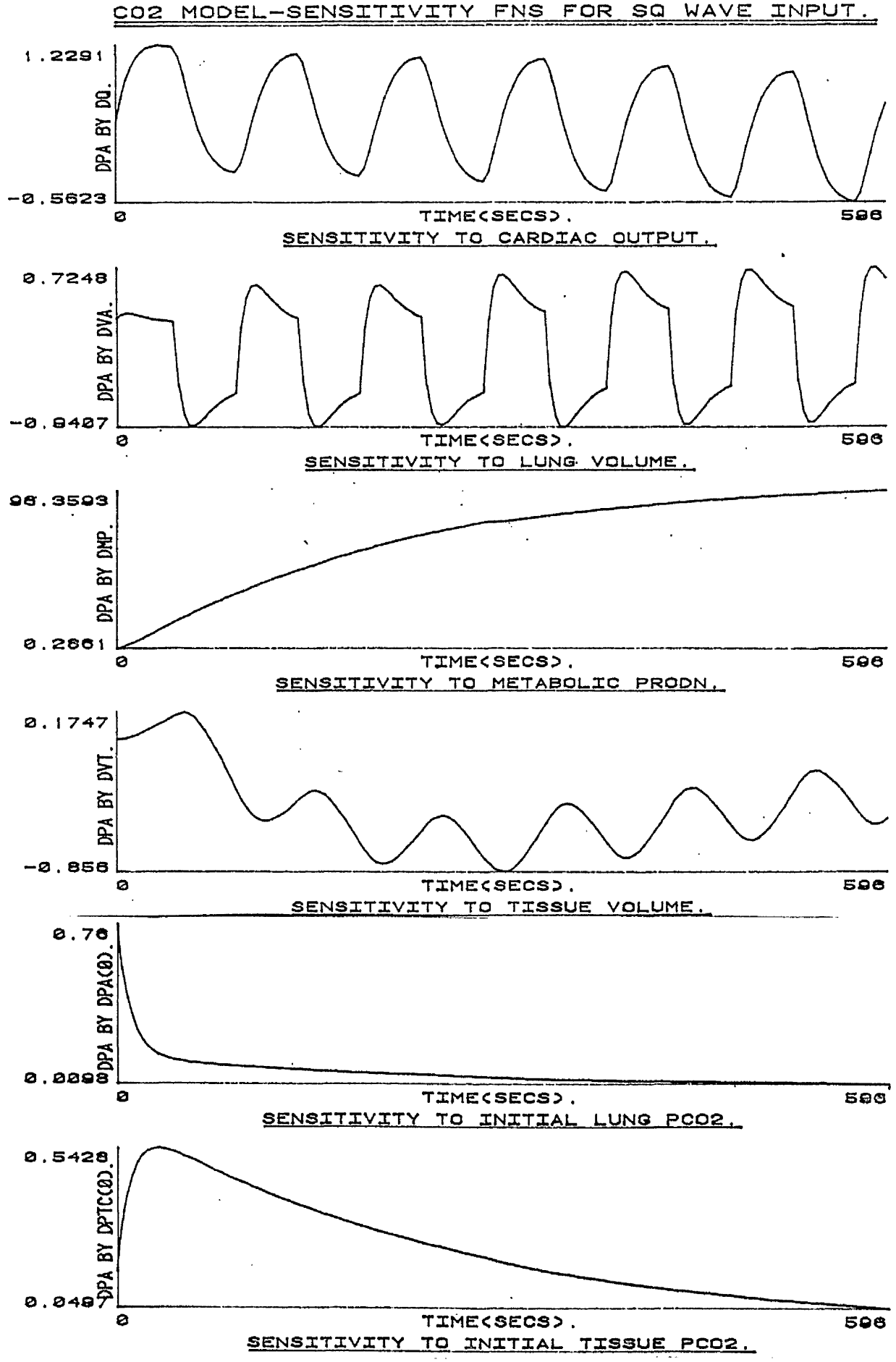

CO2 MODEL-SENSITIVITY FNS FOR SQ WAVE INPUT.
1.2291
DPA BY DQ.
-0.5623
0
TIME(SECS).
500
SENSITIVITY TO CARDIAC OUTPUT.
0.7248
DPA BY DVA.
-0.8407
0
TIME(SECS).
500
SENSITIVITY TO LUNG VOLUME.
96.3593
DPA BY DMP.
0.2661
0
TIME(SECS).
500
SENSITIVITY TO METABOLIC PRODN.
0.1747
DPA BY DVT.
-0.856
0
TIME(SECS).
500
SENSITIVITY TO TISSUE VOLUME.
0.76
DPA BY DPA(0).
0.0098
0
TIME(SECS).
500
SENSITIVITY TO INITIAL LUNG PCO2.
0.5428
DPA BY DPTC(0).
0.049
0
TIME(SECS).
500
SENSITIVITY TO INITIAL TISSUE PCO2.

FIGURE 7·4

Table 7.3

Variation of Sum of Squared Model Sensitivities to $\dot{Q}$ with CO_2 Switching Period

Period (in breaths)	$\sum_{i=1}^{M} \left(\frac{\partial Y_{M_i}}{\partial \dot{Q}} \right)^2$
12	898
16	1136
18	1257
20	1403
24	1608
28	1790
30	1856
34	2022
36	2005
40	2152
46	2208
54	2348
56	2359
60	2451

TEST SIGNAL OPTIMALITY CRITERIA VS LOZ SWITCHING PERIOD ASSUMING FIRST ORDER ARMA NOISE MODEL

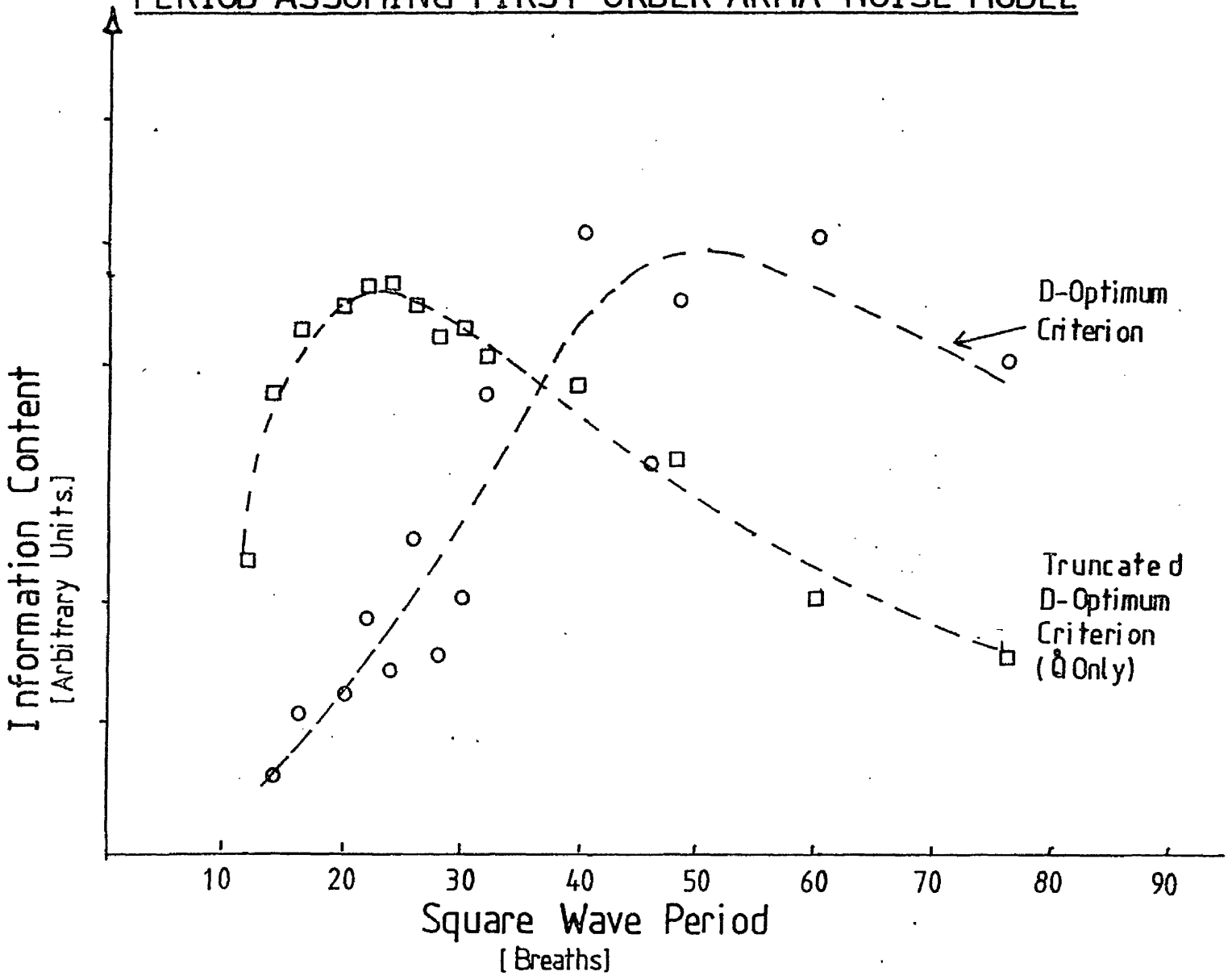


FIGURE 7·5

7.5 Implications for Other Forms of Gas Transport Model

Before going on to implement the experiments designed in the previous section for the homogeneous CO_2 model it was considered appropriate to investigate other types of gas exchange model in which cardiac output also appears as a parameter. Recall that such models describing oxygen and inert gas transport were discussed in Chapter 2.

It was felt to be particularly relevant to investigate the suitability of the oxygen model since O_2 concentration has already been recorded in the earlier validation experiments. This thus raises the possibility of fitting a coupled CO_2 - O_2 model to this data.

From Chapter 2 the O_2 model equations similar to CO_2 are as follows :-

$$\frac{V_A \, d P_A}{dt} = S \dot{V} (P_I^* - P_A) + \dot{Q} (C_{T_C} - C_A) \text{ const} \qquad 7.13$$

$$\frac{V_T \, d C_{T_C}}{dt} = - \dot{M}_D - \dot{Q} (C_{T_C} - C_A) \qquad 7.14$$

Note that in equation 7.14 the term $\dot{M}_D$, the metabolic demand, replaces the metabolic production term $\dot{M}$ present in the analogous CO_2 model equation. C_A is obtained from P_A via the O_2 dissociation curve which was discussed in Chapter 2.

A simulation programme (LUNG 2) was written to investigate the potential of the O_2 model for cardiac output estimation. This was analogous to that described for the CO_2 model in the previous section and also employed a cyclic representation of ventilation.

Using this simulation the model was subjected to hypoxic steps and square waves to determine the suitability of these test signals for estimating

cardiac output. The results obtained were very revealing. The sensitivity plots obtained for the step and square wave inputs for the 6 parameter model are given in Figures 7.6 and 7.7 respectively. Parameter values used were similar to those chosen for the CO_2 model in Table 7.1.

Notice that the form of sensitivity curve for cardiac output for both the step and the square wave input are qualitatively similar. This is in marked contrast to the analagous sensitivity curves for the CO_2 model (see Figures 7.3 and 7.4). Note also for the O_2 model that the sensitivities for $\dot{Q}$ and $C_{T_{C(0)}}$ appear to be linearly dependent. In fact, for all forms of experiment the correlation coefficient between these two parameters was found to be greater than 0.99. Thus, disappointingly the model is unidentifiable along these parameter directions. This unidentifiability of the O_2 model can in fact be largely explained in terms of the sigmoid shape of the O_2 dissociation curve. The highly non-linear shape of this curve although a positive benefit in terms of increasing the efficiency of gas exchange is a barrier in terms of accurate identification.

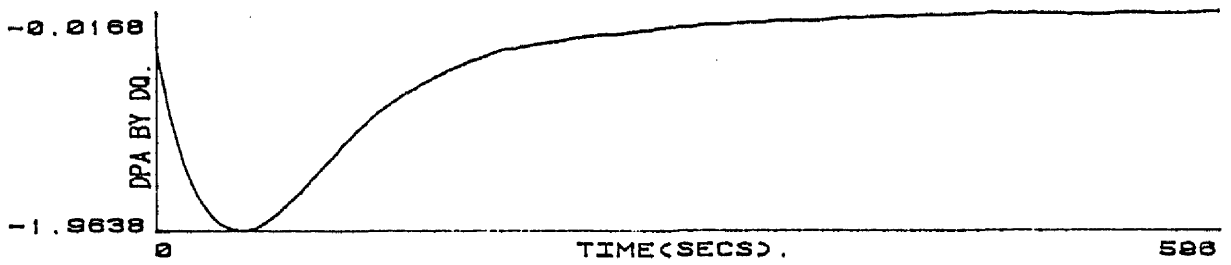
Despite using quite large hypoxic steps, the forms of experiment investigated above are still such that, in terms of alveolar gas levels, we are still operating on the relatively flat upper portion of the curve, i.e. the content-partial pressure relationship is given by :-

$$C_A(P_A) \qquad \text{const} = c \tag{7.15}$$

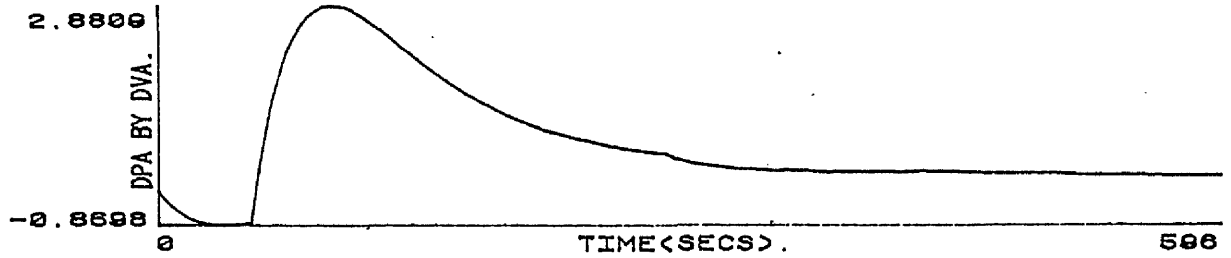
By substituting this expression in the model equations 7.13 and 7.14, and taking Laplace transforms, after some manipulation we arrive at the following.

$$P_{A(S)} = \frac{(b_1 S + b_2)U(S)}{S^2 + a_1 S + a_2} + \frac{(C_1 S + C_2)}{S^2 + a_1 S + a_2} + \frac{d_1}{S} \tag{7.16}$$

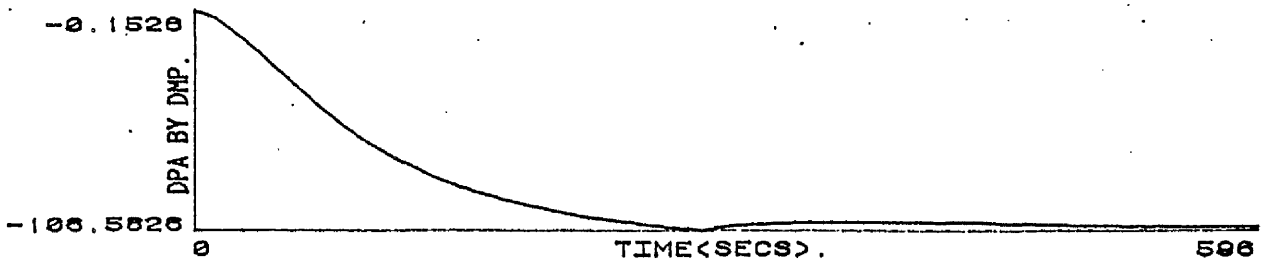
O2 MODEL-SENSITIVITY FNS FOR STEP INPUT.



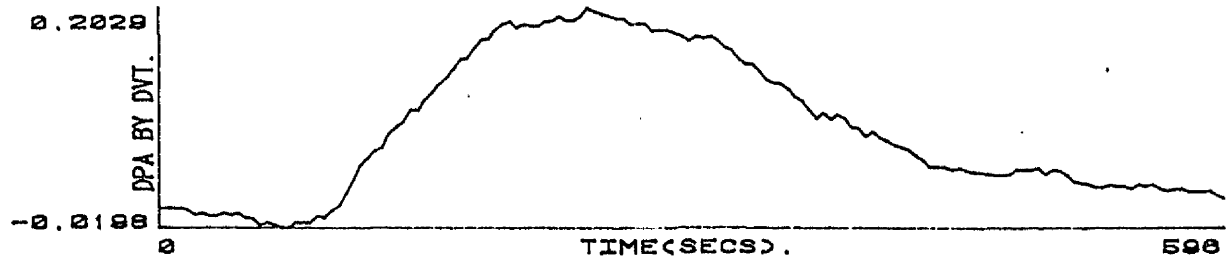
SENSITIVITY TO CARDIAC OUTPUT.



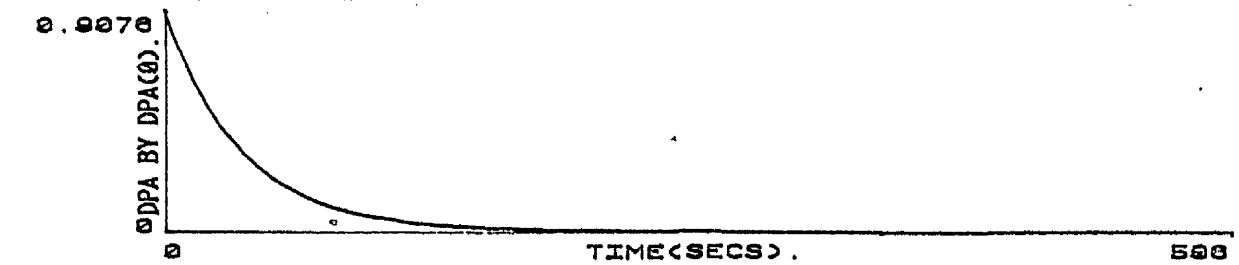
SENSITIVITY TO LUNG VOLUME.



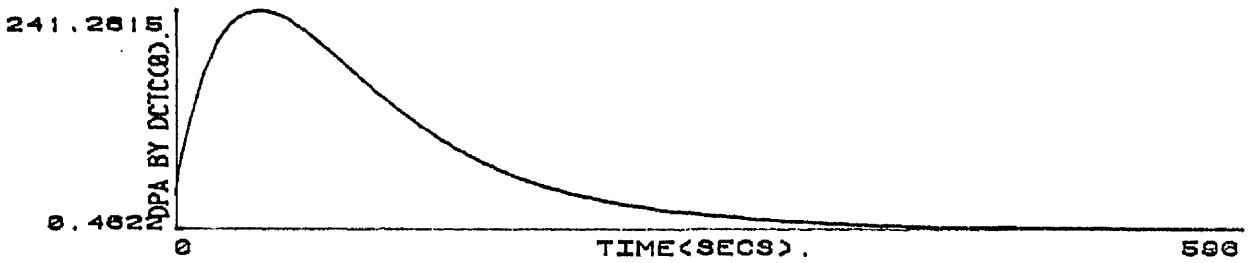
SENSITIVITY TO METABOLIC PRODN.



SENSITIVITY TO TISSUE VOLUME.



SENSITIVITY TO INITIAL LUNG PO2.



SENSITIVITY TO INITIAL TISSUE O2 CNCN.

FIGURE 7·6

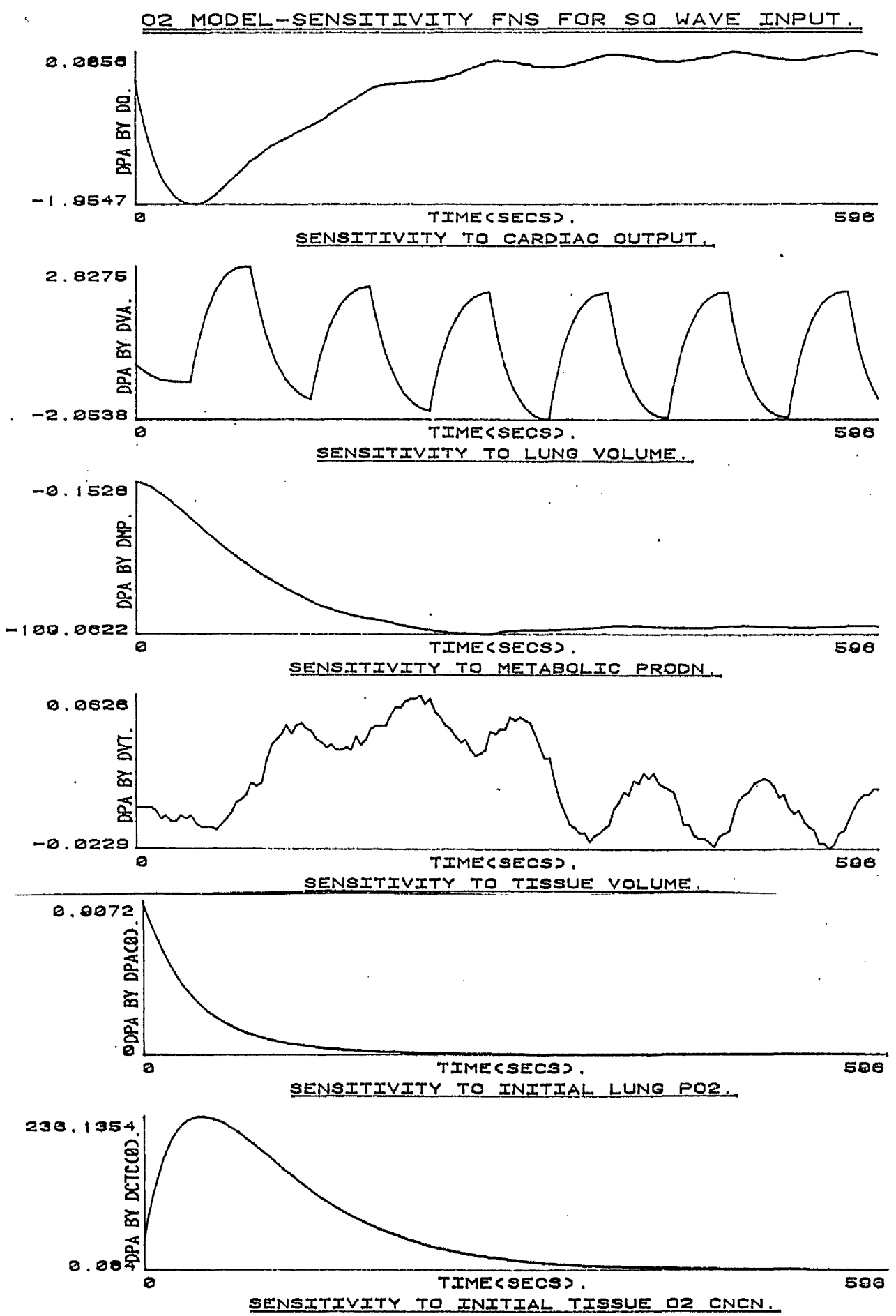

O2 MODEL-SENSITIVITY FNS FOR SQ WAVE INPUT.
0.0056
DPA BY DQ.
-1.9547
0
TIME(SECS).
500
SENSITIVITY TO CARDIAC OUTPUT.
2.8275
DPA BY DVA.
-2.0538
0
TIME(SECS).
500
SENSITIVITY TO LUNG VOLUME.
-0.1528
DPA BY DMP.
-109.0622
0
TIME(SECS).
500
SENSITIVITY TO METABOLIC PRODN.
0.0626
DPA BY DVT.
-0.0229
0
TIME(SECS).
500
SENSITIVITY TO TISSUE VOLUME.
0.0072
DPA BY DPA(0).
0
TIME(SECS).
500
SENSITIVITY TO INITIAL LUNG PO2.
236.1354
DPA BY DCTC(0).
0.00
0
TIME(SECS).
500
SENSITIVITY TO INITIAL TISSUE O2 CNCN.

FIGURE 7·7

The Laplace transform coefficients are given by

$$a_1 = \frac{\dot{Q}}{V_{TC}} + \frac{\dot{V}}{V_A} \qquad 7.17$$

$$a_2 = \frac{\dot{V}\dot{Q}}{V_A V_{TC}} \qquad 7.18$$

$$b_1 = \frac{\dot{V}}{V_A} \qquad 7.19$$

$$b_2 = \frac{\dot{V}\dot{Q}}{V_A V_{TC}} \qquad 7.20$$

$$C_1 = P_{A(0)} + \frac{\text{const } \dot{M}_D}{\dot{V}} \qquad 7.21$$

$$C_2 = \frac{\dot{Q}}{V_{TC}} P_{A(0)} + \frac{\text{const } \dot{Q}}{V_A}\left[C_{T_C}(0) - c\right] + \frac{\text{const } \dot{M}_D}{\dot{V}}\left[\frac{\dot{Q}}{V_{TC}} + \frac{\dot{V}}{V_A}\right] \qquad 7.22$$

Recall from section 4 of Chapter 4 that the above model is identifiable if the set of equations 7.16 - 7.22 have a unique solution. However, it is immediately seen from the above set of equations that any change in $C_{T_C}(0)$ can be exactly compensated for by a change in $\dot{Q}$ and V_{TC}. This thus explains the identifiability problem.

On this basis one is forced to conclude that there is little advantage to be gained in using either an O_2 or coupled O_2 - CO_2 model in order to estimate cardiac output since the O_2 model's informational properties are so poor.

A simulation programme (LUNG 3) was also written based on the equations for an inert gas transport model, i.e.

$$V_A \frac{dP_A}{dt} = S\dot{V}(P_I^* - P_A) + \alpha'_{BL}\dot{Q}(P_{T_C} - P_A) \qquad 7.23$$

$$V_{T_C} \frac{dP_{T_C}}{dt} = -\dot{Q}(P_{T_C} - P_A) \qquad 7.24$$

α'_{BL} is the Ostwald solubility coefficient between blood and lungs as defined in Table 2.1. As discussed in Chapter 2, an advantage of this form of model is that the gas content - partial pressure relationship obeys Henry's Law and is, therefore, linear. Also initial conditions in the two compartments are generally known á priori to be zero since normally a gas is used which is not normally resident in the human body. Thus the above model has only three unknown parameters since no metabolic uptake or production term exists for inert gases. No identifiability problems were found to exist for the inert gas model, which was encouraging. To compare the potential of this form of model for cardiac output estimation as opposed to the CO_2 model, the value of the information measures obtained from this model for differing solubility coefficients was compared with that obtained from the same experiment using the CO_2 model. The form of experiment used was that which was shown to be optimal for the CO_2 model in a previous section (i.e. switching period 24 breaths). The results are given in Table 7.4. These indicate that a value of solubility coefficient in the range $2 \rightarrow 4$ is appropriate for estimating cardiac output. Thus, since this corresponds roughly to the effective solubility of CO_2 (i.e.$\approx$ bB) there does not seem to be any great benefit to be gained by using exotic inert gases.

Table 7.4

Comparison of Information Criterion Indicating a Good Experiment for Cardiac Output Estimation for Inert Gas Models of Varying Solubility and CO_2 and O_2 Model

Value of Bunsen Solubility Coeff.	Information Measure for $\dot{Q}$
0.006	0.037
0.47 (Nitrous Oxide)	104.16
2.4 (Halothane)	666.67
$\approx$ 3.7 (CO_2 model (4 PARS))	625.03
O_2 model (4 PARS)	4.00

7.6 Reproducibility Results Using the Improved Form of Experiment

Having confirmed in the previous section that there is no great advantage to be gained in respect of cardiac output estimation by using another type of model, these alternative models can thus be justifiably dismissed as regards this particular application and attention once again focussed on the homogeneous CO_2 model.

In section 7.4 a form of experiment was designed to perturb this model which, at least in theory, should result in a more reproducible technique for cardiac output estimation than that previously obtained. In early 1979 a series of trials were undertaken to test this theory. This section describes the results.

It was originally envisaged that these experiments would take the form of a further set of validation studies (i.e. carrying out our method simultaneously with the dye technique). However, arranging this sort of experiment is a time-consuming process since obtaining subjects is difficult. Also it is necessary to ensure attendance of skilled medical personnel to carry out the potentially hazardous dilution experiments. Thus it was ultimately decided a better strategy, for an initial trial phase, would be to concentrate on doing multiple measurements of the non-invasive technique by itself on single subjects. Although this will not allow us to obtain any ideas of absolute accuracy of the technique, it does allow reproducibility to be assessed which is of prime concern. Since this strategy involves smaller overheads in terms of personnel, more experiments can be carried out in a shorter time, and it allows at least a first assessment of the worth of the new technique.

At the time of writing 20 sets of Reproducibility Studies have been carried out on young, healthy volunteer subjects (both male and female) from

the Centre of Respiratory Investigation, Glasgow Royal Infirmary and the Department of Electronics and Electrical Engineering, University of Glasgow. These studies consisted of a maximum of four runs on each experimental subject, each carried out sequentially on the same afternoon. For ease of implementation, the test signal used in all but one of the series of studies consisted of 1 min alternating between air and 7/5% CO_2 . This period was found to be convenient for manual operation of the gas valves. Of the 20 datasets, 8 had to be discarded due to data sampling problems (teething troubles with the new mass spectrometer and expired flowmeter) leaving 12 useful sets of data (47 individual estimation runs) to form a basis of comparison with the earlier validation results.

The estimates and their respective variances obtained by fitting six and eight parameter models to the data are given in Appendix E. Even a brief glance at these results shows that the reproducibility of the estimates have been tightened up as compared to the validation data. This will be discussed a little later, however. The reproducibility of the maximum likelihood results also tend to be better than the ordinary least squares estimates. This means the noise model is important for these experiments. It is exceedingly difficult to place a physical interpretation on the noise model but, intuitively, it is felt to be associated with the marked change in a subject's ventilatory pattern which inevitably occurs over the course of an experiment due to the hypercapnic stimulation of the respiratory controller. As in Chapter 4, the most appropriate model order was tested for using the F-ratio test and Akaikes method. These results are given in Table 7.5. They show that in every case but one (REPO83) the increase in model order from six to eight was significant at the 5% level, using the F-ratio test and

Table 7.5

MODEL ORDER TESTS

Reproducibility Data

File	N	$\Sigma e_{i\,6}^2$	$\Sigma e_{i\,8}^2$	f6→8	F6→8	AIC_6	AIC_8	Chosen Order
REPØ11	144	40.79	18.89	78.84	3.0	238.9	132.09	8,8
3	157	39.56	25.70	40.18	3.0	241.05	177.33	8,8
4	183	45.62	27.41	58.13	3.0	277.03	187.80	8,8
REPØ21	167	38.44	11.50	186.23	3.0	240.53	43.00	8,8
2	200	60.05	28.45	106.62	3.0	338.85	193.44	8,8
4	163	55.66	15.55	199.90	3.0	299.35	95.49	8,8
5	189	70.46	19.40	238.19	3.0	361.77	122.00	8,8
REPØ71	126	37.88	18.70	60.51	3.0	218.07	133.13	8,8
2	129	55.13	28.38	57.03	3.0	268.35	186.70	8,8
3	131	44.76	25.14	48.00	3.0	243.02	171.45	8,8
4	128	31.72	22.57	24.32	3.0	196.61	157.05	8,8
REPØ81	128	15.67	11.92	18.88	3.0	106.35	75.34	8,8
2	135	19.10	15.36	15.46	3.0	131.04	105.62	8,8
3	145	33.64	F.M.	-	3.0			6
4	157	54.17	35.13	40.38	3.0	290.40	226.41	8,8
REPØ91	148	27.51	18.49	34.15	3.0	182.90	128.09	8,8
2	153	63.23	39.95	42.25	3.0	310.92	244.67	8,8
3	153	37.08	22.32	47.94	3.0	229.26	155.60	8,8
4	155	43.90	27.21	45.08	3.0	256.26	186.12	8,8
REP 111	136	71.16	55.70	17.76	3.0	309.79	280.48	8,8
2	146	57.02	38.33	33.64	3.0	288.99	234.99	8,8
3	148	80.34	56.76	29.08	3.0	341.51	294.09	8,8
4	142	64.85	33.17	35.64	3.0	303.61	212.41	8,8
REP 121	143	37.30	24.15	36.75	3.0	225.57	167.41	8,8
2	146	78.61	45.77	49.51	3.0	335.87	260.89	8,8
3	151	154.39	50.91	145.3	3.0	443.80	280.27	8,8
4	162	88.50	40.10	92.94	3.0	373.71	249.47	8,8
REP 141	135	35.81	23.42	33.59	3.0	215.89	162.57	8,8
2	147	27.75	16.50	47.38	3.0	184.02	111.59	8,8
3	160	43.56	23.34	65.84	3.0	257.81	161.98	8,8
4	167	33.55	22.36	39.78	3.0	217.81	154.05	8,8
REP 151	151	44.36	29.01	37.83	3.0	255.48	195.35	8,8
2	149	52.33	47.97	6.41	3.0	278.86	269.89	8,8
3	144	27.06	20.47	21.89	3.0	179.85	143.66	8,8
4	142	38.15	32.10	12.62	3.0	228.28	207.76	8,8
REP 181	144	34.03	19.83	48.69	3.0	212.85	139.08	8,8
2	171	41.30	23.00	64.84	3.0	254.23	160.44	8,8
3	158	48.18	21.11	96.17	3.0	272.65	146.27	8,8
4	154	42.64	15.69	125.39	3.0	251.19	101.23	8,8

continued .....

Table 7.5

MODEL ORDER TESTS

Reproducibility Data cont'd.....

File	N	$\Sigma e_{i\,6}^2$	$\Sigma e_{i\,8}^2$	f 6→8	F 6→8	AIC_6	AIC_8	Chosen order
REP191	142	24.41	12.95	59.29	3.0	164.86	78.85	8,8
2	147	37.26	20.09	59.40	3.0	227.33	140.53	8,8
3	161	50.52	21.09	106.75	3.0	282.21	145.56	8,8
4	153	48.34	13.92	179.27	3.0	269.83	83.36	8,8
REP201	115	20.19	9.69	117.03	3.0	179.93	57.80	8,8
2	138	26.69	13.28	65.63	3.0	176.82	84.50	8,8
3	118	12.25	8.02	29.00	3.0	79.52	33.53	8,8
4	143	20.69	12.02	48.68	3.0	141.29	67.63	8,8

also resulted in a smaller value of Akaikes criterion. Notice that these test results are more powerful statistically than those obtained in the validation data. In fact, for the F-ratio test the increase in model order was still significant in the same number of cases at the 1% significance level.

These model order results are also confirmed by tests on the independence of the residuals which are summarised in Table 7.6. For the six parameter model the residuals in every case are correlated, both on the basis of the test on the number of runs and on the number of points outside the $2\hat{\sigma}$ limit. However, for the eight parameter results only 2/47 results appear to be correlated on the basis of both of these tests. This tends to suggest the eight parameter model is adequate. Typical fits obtained using the six and eight parameter models on file REPO21 are shown in Figures 7.8 and 7.9 respectively.

The new experiments were found to result in identifiability of the model parameters being increased in comparison with the earlier validation experiments, as was hoped for. For example, consider the following typical parameter correlation matrix R obtained for the eight parameter fit to file REPO21 which is shown below.

$$R = \left[\begin{array}{cc|cccccc} & & \multicolumn{6}{c}{\text{noise model parameters}} \\ 1 & & & & & & & \\ 0.53 & 1 & \multicolumn{6}{c}{\text{deterministic model parameters}} \\ \hline -0.027 & -0.029 & 1 & & & & & \\ -0.065 & 0.080 & -0.43 & 1 & & \multicolumn{3}{c}{\text{Symmetric}} \\ 0.047 & 0.031 & 0.036 & 0.067 & 1 & & & \\ -0.22 & -0.070 & -0.20 & 0.42 & -0.017 & 1 & & \\ 0.013 & -0.025 & 0.021 & -0.15 & -0.010 & -0.018 & 1 & \\ 0.057 & +0.038 & -0.54 & 0.20 & -0.20 & -0.005 & -0.31 & 1 \end{array}\right]$$

Table 7.6
Reproducibility Data

Tests On Independence of Residuals

FILE	6 PAR LEAST SQUARES			8 PAR MAXIMUM LIKELIHOOD		
	No. of runs test value	No. of points outside $1\hat{\sigma}$ limit for ACF	Correlated	No. of runs test value	No. of points outside $1\hat{\sigma}$ limit for ACF	Correlated
REP011	-4.900	10/30	Y	-1.874	7/30	N
3	-5.109	10/30	Y	0.346	8/30	N
4	-6.498	10/30	Y	-0.527	5/30	N
REPØ21	-7.504	10/30	Y	-0.151	5/30	N
2	-7.017	10/30	Y	-0.694	6/30	N
4	-7.351	10/30	Y	1.262	7/30	N
5	-9.321	10/30	Y	-0.729	7/30	N
REPO71	-7.245	10/30	Y	-0.064	9/30	N
2	-5.400	10/30	Y	-0.587	7/30	N
3	-5.084	9/30	Y	0.375	9/30	N
4	-4.171	10/30	Y	-0.619	8/30	N
REPO81	-5.198	10/30	Y	0.278	8/30	N
2	-3.728	10/30	Y			
3	-6.085	8/30	Y/N			
4	-6.333	9/30	Y	-1.526	5/30	N
REPO91	-7.340	10/30	Y	-1.064	9/30	N
2	-7.534	10/30	Y	-0.969	4/30	N
3	-5.029	10/30	Y	-0.120	5/30	N
4	-6.210	10/30	Y	-1.395	6/30	N
REP111	-6.187	10	Y	-4.537	7/30	N/Y
2	-5.054	10	Y	1.119	9/30	N
3	-6.515	10	Y	-2.513	11/30	Y
4	-5.800	10	Y	-0.243	8/30	N
REP121	-5.692	10	Y	1.059	9/30	N
2	-7.282	10	Y	-1.546	12/30	Y/N
3	-6.203	10	Y	0.654	3/30	N
4	-7.141	10	Y	-1.017	3/30	N
REP141	-6.059	10	Y	-2.418	5/30	Y/N
2	-6.277	10	Y	-2.313	11/30	Y
3	-7.186	10	Y	-1.664	4/30	N
4	-4.812	10	Y	-1.951	8/30	N
REP151	-6.585	10	Y	-1.496	3/30	N
2	-5.582	10	Y	-2.925	6/30	Y/N
3	-3.260	9	Y	-0.251	4/30	N
4	-2.777	10	Y	-1.346	8/30	N

continued .....

Table 7.6

Reproducibility Data

Tests on Independence of Residuals cont'd.....

FILE	6 PAR LEAST SQUARES			8 PAR MAXIMUM LIKELIHOOD		
	No. of runs test value	No. of points outside $1\hat{\sigma}$ limit for ACF	Correlated	No. of runs test value	No. of points outside $1\hat{\sigma}$ limit for ACF	Correlated
REP181	-5.041	10/30	Y	-0.983	2/30	N
2	-6.898	10/30	Y	-0.920	6/30	N
3	-7.419	10/30	Y	-0.168	5/30	N
4	-7.326	10/30	Y	1.134	9/30	N
REP191	-4.426	10/30	Y	0.087	7/30	N
2	-6.952	10/30	Y	-1.146	7/30	N
3	-7.725	10/30	Y	-0.316	6/30	N
4	-8.598	10/30	Y	-1.207	9/30	N
REP2O1	-6.655	10/30	Y	-1.483	10/30	N
2	-6.750	10/30	Y	0.259	6/30	N
3	-4.900	10/30	Y	-1.504	10/30	N
4	-6.839	10/30	Y	-0.963	3/30	N

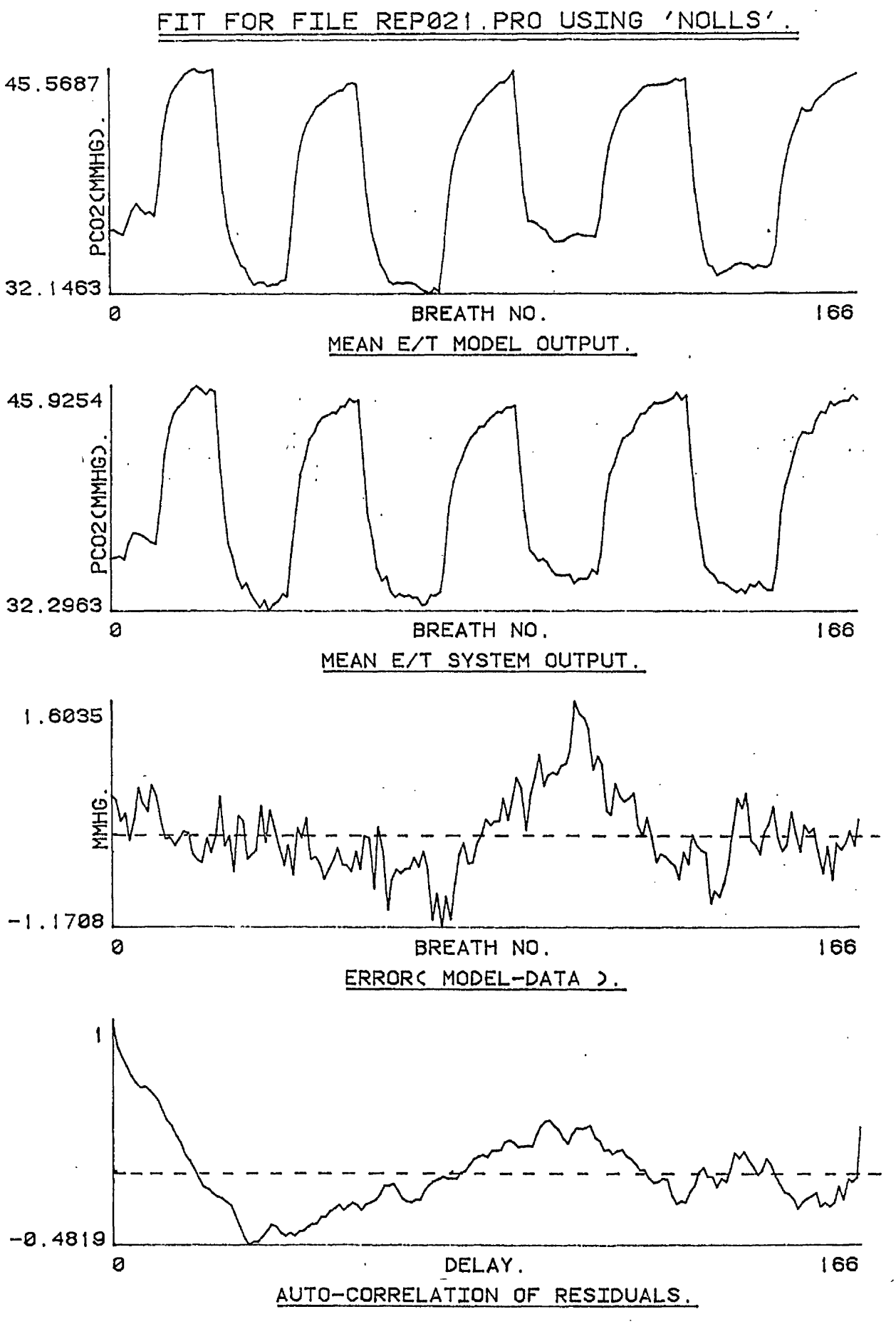

FIT FOR FILE REP021.PRO USING 'NOLLS'.
45.5687
PCO2(MMHG).
32.1463
0
BREATH NO.
166
MEAN E/T MODEL OUTPUT.
45.9254
PCO2(MMHG).
32.2963
0
BREATH NO.
166
MEAN E/T SYSTEM OUTPUT.
1.6035
MMHG.
-1.1708
0
BREATH NO.
166
ERROR(MODEL-DATA).
1
-0.4819
0
DELAY.
166
AUTO-CORRELATION OF RESIDUALS.

FIGURE 7·8

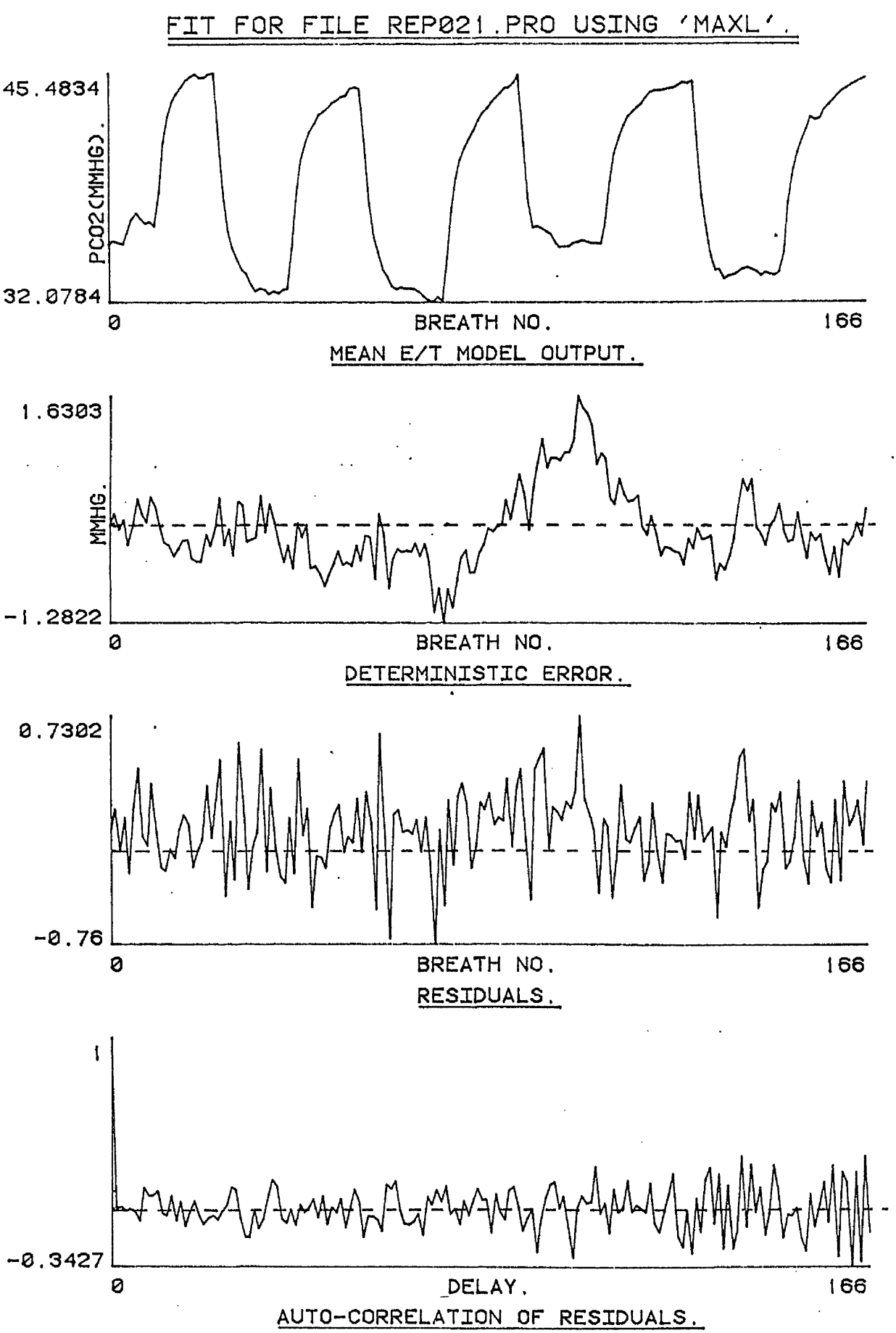

FIT FOR FILE REP021.PRO USING 'MAXL'.
45.4834
PCO2(MMHG).
32.0784
0
BREATH NO.
166
MEAN E/T MODEL OUTPUT.
1.6303
MMHG.
-1.2822
0
BREATH NO.
166
DETERMINISTIC ERROR.
0.7302
-0.76
0
BREATH NO.
166
RESIDUALS.
1
-0.3427
0
DELAY.
166
AUTO-CORRELATION OF RESIDUALS.

FIGURE 7·9

Notice that the large $\dot{M} / V_{T_C}$ interaction prevalent in the earlier validation results has been reduced. More importantly, the correlation of $\dot{Q}$ with the other model parameters, noteably the initial conditions $P_A(0)$ and $P_{T_C}(0)$ have also been markedly reduced. The noise model parameters are again independent of the deterministic model parameters as expected.

We will now discuss the reproducibility of the estimates in comparison with that obtained from the validation data. This is, after all, the matter of prime concern. These results are given in Table 7.7. Although these results indicate that the observed sample variances still cannot attain the Cramer-Rao lower bound they are still extremely encouraging as they bear out the predicted increase in reproducibility of the non-invasive cardiac output estimation technique by going to this new form of experiment. Notice that the reproducibility of all the estimates has been markedly improved in comparison with previous results (and that of $\dot{M}$ and V_{T_C} especially so). The average reproducibility of $\dot{Q}$ from these studies was found to be 6.2% Recall the average reproducibility of $\dot{Q}$ from the validation experiments (from Chapter 4) was 12.2% and that from the dye dilution estimates themselves was only 6.8%. Thus, on the basis of this comparison the ultimate attractiveness of the new form of experiment begins to look very promising.

Notice from the 12 sets of results that the $\dot{Q}$ reproducibility is frequently better than 5%. However, 2 sets of runs REP08 and REP15 are rather disappointing and tend to mar the overall picture which is otherwise much better. This tended to suggest that these particular results might be a bit dubious in some way.

A significant factor concerning these 2 datasets is that they were both carried out on the same (female) subject (each on a different afternoon). In addition, these were the only two sets of runs in which

Table 7.7

Reproducibility Data

Average Predicted Variances vs Observed Sample Variances

DATASET		$\dot{Q}$	VA	$\dot{M}$	V_{T_C}
REPØ1	predicted	0.21	0.10	4.4×10^{-3}	0.24
	actual	0.15	0.08	7.7×10^{-3}	0.28
	CV (%)	2.2	2.8	2.6	7.9
REPØ2	predicted	0.26	0.13	5.6×10^{-3}	0.30
	actual	0.30	0.30	9.8×10^{-3}	0.55
	CV (%)	5.1	10.8	4.0	16.0
REPØ7	predicted	0.35	0.23	3.5×10^{-3}	0.7
	actual	0.30	0.35	8.2×10^{-3}	0.5
	CV (%)	4.8	10.2	3.4	11.3
REPØ8	predicted	0.24	0.17	2.0×10^{-3}	0.65
	actual	0.69	0.53	6.6×10^{-3}	0.48
	CV (%)	12.3	17.1	3.1	10.8
REPØ9	predicted	0.36	0.17	3.3×10^{-3}	0.22
	actual	0.60	0.37	10.4×10^{-3}	0.42
	CV (%)	10.2	11.3	5.1	15.8
REP 11	predicted	0.30	0.18	3.5×10^{-3}	0.16
	actual	0.25	0.19	14.9×10^{-3}	0.34
	CV (%)	4.6	6.0	7.4	13.6
REP 12	predicted	0.35	0.16	4.5×10^{-3}	0.29
	actual	0.16	0.33	12.5×10^{-3}	0.65
	CV (%)	2.3	10.4	5.1	19.4
REP 14	predicted	0.16	0.09	1.8×10^{-3}	0.22
	actual	0.22	0.24	7.5×10^{-3}	0.24
	CV (%)	4.0	11.3	3.8	6.4
REP 15	predicted	0.25	0.12	2.0×10^{-3}	0.27
	actual	1.08	0.58	7.6×10^{-3}	0.38
	CV (%)	16.4	16.7	3.6	9.2
REP 18	predicted	0.31	0.11	4.0×10^{-3}	0.13
	actual	0.37	0.43	14×10^{-3}	0.15
	CV (%)	5.4	12.1	5.2	6.3
REP 19	predicted	0.45	0.18	4.3×10^{-3}	0.26
	actual	0.31	0.28	6.1×10^{-3}	0.26
	CV (%)	4.2	7.8	2.2	8.3
REP 2Ø	predicted	0.21	0.12	1.9×10^{-3}	0.36
	actual	0.18	0.14	5.4×10^{-3}	0.34
	CV (%)	3.2	5.6	3.1	8.5
Average CV(%)		6.2	10.1	4.1	11.1

this particular subject participated.

Further scrutiny of these particular results yield a very interesting trend. In both sets of files the estimate for the first run is quite high and successive estimates into the afternoon are all successively smaller. The chances of this being a purely random phenomenon are felt to be remote. Rather it is suspected that this is a true biological variation which is being observed (i.e. this is a natural trait of the particular subject who was not in a true basal state throughout the course of the runs). In retrospect, this shows up a disadvantage of not having carried out dye cross comparisons since this phenomenon could have been detected and hence confirmed by this means.

One of the rogue datafiles REPO81 was further investigated by way of some stationarity tests. The results obtained by carrying out separate estimations over 0-6 mins and 4-10 mins of the experiment for this file and two other files chosen at random from the rest of the files were compared. These are presented in Table 7.8. This analysis also had the double advantage of allowing the stationarity of the estimates in general to be checked for the form of experiment used. (Recall in section 7.4 of this chapter some worry was expressed in terms of such a long period of CO_2 breathing increasing $\dot{Q}$ directly).

For the two files chosen at random, REPO11 and REP121 the two sets of estimates argree reasonably well with each other and with the estimates obtained from fitting over the whole file, (apart, of course, from the estimates of $P_A(0)$ and $P_{T_C}(0)$ which one would expect to be different). The different estimates are certainly well within the 95% confidence distances of each other. Stationarity can therefore safely be assumed in these cases

TABLE 7.8

Reproducibility Data - Stationarity Tests for Files REPØ1, REPØ8 and REP 12

FILE	$\dot{Q}$	VA	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	a_1	b_1	Mean square error
REPØ 11									
0 - 4½ mins	6.67	2.81	0.249	3.82	39.1	46.0	-0.891	-0.378	0.136
4½ - 9 mins	6.72	3.02	0.238	4.07	50.6	51.8	-0.216	0.148	0.109
0 - 9 mins	7.11	2.92	0.276	3.86	38.9	45.1	-0.95	-0.36	0.131
REPØ 81									
0 - 6 mins	6.91	3.17	0.217	4.65	35.4	40.4	0.256	0.580	0.057
4 - 10 mins	5.84	3.77	0.207	4.45	37.8	44.6	-0.588	-0.057	0.124
0 - 10 mins	6.43	3.62	0.213	4.47	35.4	41.2	-0.546	-0.049	0.093
REP 121									
0 - 6 mins	6.28	2.87	0.237	4.03	43.7	47.2	-0.844	-0.509	0.164
4 - 10 mins	6.42	2.87	0.217	4.25	52.9	53.3	-0.841	-0.400	0.164
0 - 10 mins	6.56	2.70	0.240	4.10	44.0	46.7	-0.900	-0.471	0.169

and it is believed on this basis in the cases of most of the rest of the data files. However, in contrast for the file REPO81 the estimates obtained over each half of the data are quite different. That is, the estimate over the first half of the data is markedly larger from that obtained over the second. This therefore confirms earlier suspicions about non-stationarity of the estimates obtained on this particular subject.

Further temporal convergence results have been obtained by successively estimating models over 2, 4, 6, 8 and 10 minutes of the data for file REPO81 and file REP121 for comparison. These are given in Table 7.9. This shows estimates of $\dot{Q}$ over successive portions of file REPO81 monotonically decrease whilts those over REP121 tend to a steady value.

The results in Table 7.9 for REP121 tend to suggest that 6 mins is a long enough observation time for adequate estimation of $\dot{Q}$ and perhaps this should be borne in mind for the future definitive validation experiments.

In conclusion, from the above discussion it is felt there are reasonable grounds for the cardiac output reproducibilities for data sets REPO8 and REP15 to be honourably discounted. On this basis, calculating a value for the average reproducibility over the rest of the filesets results in a value of 4.6%, that is, better than the reproducibility of the dye dilution results from the validation data.

Table 7.9

Reproducibility Data - Temporal Convergence for Files REPØ8 and REP 12

FILE	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	a_1	b_1	Mean Square error
REPØ81									
0 - 2 mins	8.01	2.61	0.222	4.85	35.7	38.9	1.017	1.147	0.049
0 - 4 mins	7.23	2.76	0.217	4.66	35.5	40.1	0.209	0.599	0.042
0 - 6 mins	6.91	5.17	0.217	4.65	35.4	40.4	0.256	0.580	0.057
0 - 8 mins	6.78	3.20	0.215	4.59	35.5	40.7	-0.173	0.292	0.057
0 - 10 mins	6.43	3.62	0.213	4.47	35.4	41.2	-0.546	-0.049	0.093
REP121									
0 - 2 mins	6.00	2.73	0.232	4.24	44.2	47.7	-0.99	-0.90	0.09
0 - 4 mins	5.82	2.74	0.227	3.82	43.8	48.5	-0.56	-0.52	0.163
0 - 6 mins	6.28	2.87	0.237	4.03	43.7	47.2	-0.84	-0.51	0.164
0 - 8 mins	6.32	2.78	0.238	3.80	43.4	46.8	-0.86	-0.59	0.159
0 - 10 mins	6.56	2.70	0.240	4.10	44.0	46.7	-0.90	-0.47	0.169

CHAPTER 8

DESIGN OF IDENTIFICATION EXPERIMENTS TO FACILITATE DISCRIMINATION BETWEEN HOMOGENEOUS AND INHOMOGENEOUS LUNG MODELS - A SIMULATION STUDY .

8.1 Introduction

To the people of the world today, the crippling respiratory disorders of tuberculosis and pneumonia are no longer the great dread they once were to their predecessors of the later 19th and early 20th century. Nevertheless, pulmonary diseases are still a major cause of adult morbidity. The nature of the more common respiratory disorders are illustrated schematically in Fig. 8.1 in relation to a single conducting airway with terminating alveolus.

Although the pathology of these diseases may all be different in terms of impairment of normal lung function, these disorders can be conceptualised as resulting in two basic effects. These are the maldistribution of ventilation with respect to perfusion (blood flow) in the lung and/or the opposite. For example, in atelectasis, blood is perfusing alveolar regions which are not being ventilated. This 'wasted blood flow' is known as 'venous admixture' or 'shunt'. Alternatively, oedema results in ventilation being supplied to a portion of the lung which is not being adequately perfused. This is 'wasted ventilation' and constitutes a parallel or 'alveolar dead space' (75, 221). In fact, these inhomogeneities exist even in the normal subject, e.g. the supraclavicar regions of the lung where the pressure in the pulmonary arterioles is less than atmospheric resulting in collapse in this region; this is in effect alveolar deadspace. Also, part of the bronchial flow together with the venae cordis minimae of the left heart constitute a shunt. However, inevitably the effect of inhomogeneity is more pronounced in pathological conditions.

It can be shown that the presence of significant degrees of venous admixture or alveolar deadspace has a deleterious effect on the efficiency of gas

SCHEMATIC DIAGRAM OF COMMON RESPIRATORY DISORDERS

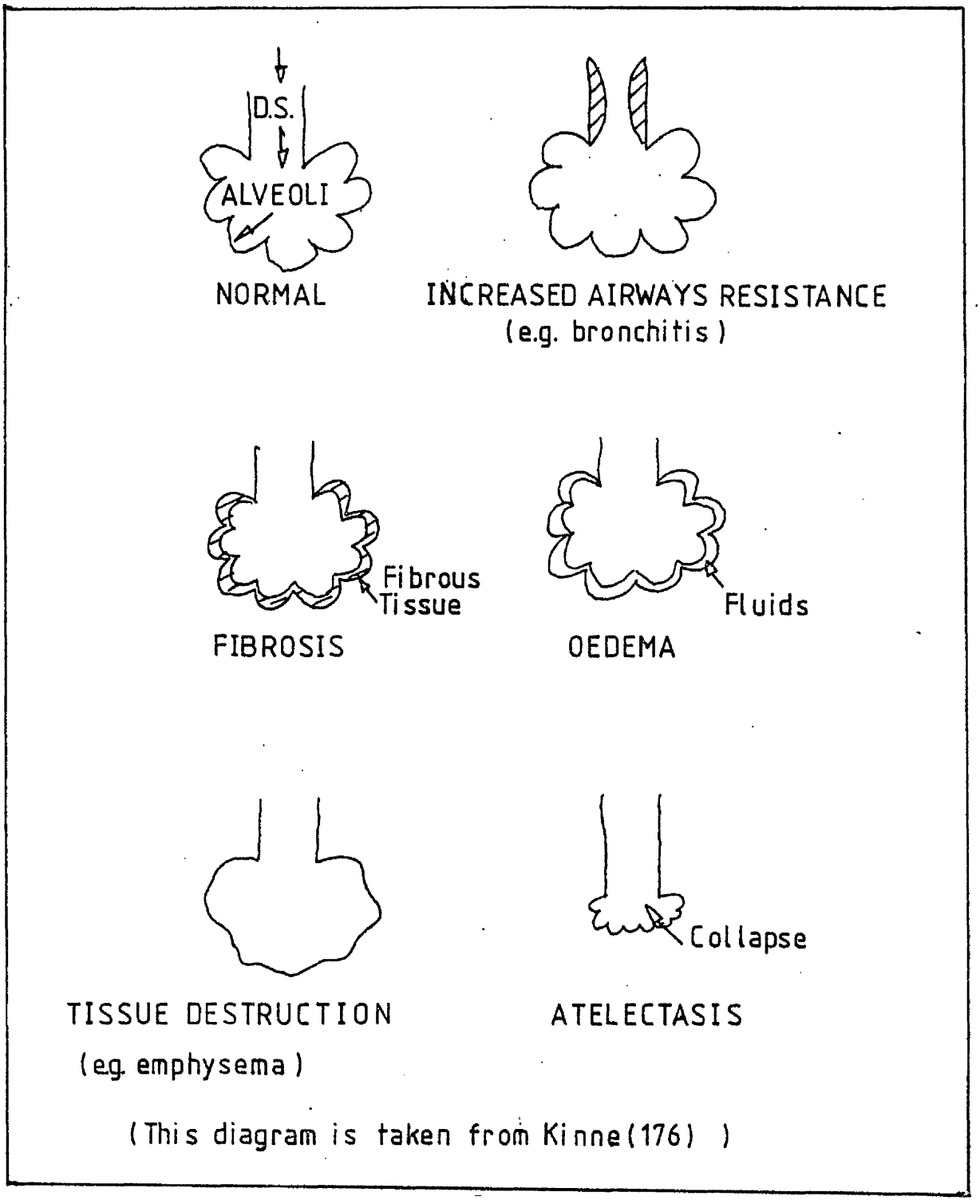


FIGURE 8·1

transport in the lungs. (For a more detailed exposition of this see West (294), Chapter 4.) This means that, in a resting state a chronic bronchitic for example, must expend more energy to maintain adequate blood gas levels than the equivalent person with normal lung function.

Most of these diseases are irreversible in that tissue once destroyed cannot be restored. However, they can be arrested and the symptoms at least temporarily relieved given an early diagnosis. Thus, in this respect, a sensitive test of pulmonary function suitable for mass screening purposes would be an immensely useful clinical tool. Although radioactive tracer experiments (20, 209, 295) have yielded very useful results on distributions of ventilation and blood flow in the lungs, unfortunately they are not entirely suitable for this purpose.

Thus, having identified the need for a simple technique for early detection of lung inhomogeneity, this chapter explores one approach to this problem via the use of mathematical models and identification techniques.

In the discussion above we have implicitly inferred three types of structure in the diseased lung (alveolar dead space, shunt and ideal gas exchanging area). Therefore, parsimonious models of such a lung must also reflect these three basic facets. Thus, for this purpose an inhomogeneous inert gas model is used, which is a variant of the form of dynamic models with time-varying ventilation described in Chapter 2. The basis of such a model is outlined by Pack (228) and is in fact a dynamic version of the classic steady state model first suggested by Riley and Cournand (245, 246). It was decided to use an inert gas model in this work to aleviate difficulties with the mathematical complications of the O_2 or CO_2 dissociation curves (see Chapter 2) and subsequently simplifying the model by avoiding the need to include a metabolic term in the equations.

Although the model itself is not original, the idea behind its utilisation in the proposed new test of pulmonary function is felt to be novel. The new technique relies on using an extension of the design techniques discussed in Chapter 7 to evolve dynamic experiments which resolve the ambiguities between the homogeneous and inhomogeneous gas exchange models. Thus, when each of these models are fitted in turn to the resultant patient data from these experiments and a test of model structure (see Chapter 4) used to discern which model is appropriate to the current patient data, this structure test will be rendered optimally powerful and hence hopefully very sensitive.

The method as well as being a test of model structure also permits quantitive assessment of the degree of inhomogeneity in terms of the volume of the alveolar deadspace. However, care has to be taken as to how this quantity is interpreted as it is conceptual rather than anything physical (i.e. the lung is in reality a continuum of different compartments (alveoli) with a corresponding continuous distribution of $\dot{V}/\dot{Q}$ ratios.) In comparison, our model effectively assumes this structure to be lumped into three compartments with $\dot{V}/\dot{Q}$ ratios of 0, 1 and infinity. In clinical terms this is not necessarily disadvantageous since the standard steady-state tests of pulmonary index (e.g. (119)) are equally conceptual. All it means is that a period of assimilation with the new technique will be necessary before it can be used as an effective tool.

This chapter then describes a preliminary theoretical investigation of the feasibility of this new technique although, unfortunately, time has not permitted any practical experiments to be carried out.

In Section 8.2 of this chapter the published literature on mathematical models describing inhomogeneous lungs and their application in

quantitive assessment of lung disfunction is reviewed. In section 8.3 the inhomogeneous inert gas transport model is presented and the identifiability aspects of this model are discussed in section 8.4. Section 8.5 introduces the necessary extensions of the theory of Chapter 7 to design experiments for model structure discrimination. Finally, in section 8.6 this theory is utilised to design an experiment to discriminate between the homogeneous and inhomogeneous model for a reasonable *a priori* set of parameters and the implications of this are discussed.

8.2 Inhomogeneous Gas Transport Models Review

Many types of models, both dynamic and steady-state have been used to describe gas transport in the lungs in conditions of abnormality. As briefly mentioned in the introduction, the first significant contribution to modelling lung inhomogeneity was the work of Riley and Cournand (246) (subsequently known as the 'Riley analysis').

This analysis allowed percentage shunt or venous admixture ($\dot{Q}$ shunt / $\dot{Q}$ total) to be calculated from steady state measurements of arterial and mean end-expiratory CO_2 partial pressures and percentage alveolar deadspace ($V_{alv\ d}$ / $V_{tidal\ vol}$) to be calculated from steady-state measurements of end-expiratory, mixed veneous and arterial O_2 concentrations.

Although the above analysis has been widely used Kelman (172) has shown it to be sensitive to measurement errors. (Many of these errors can be traced to the deleterious assumptions about ventilation necessitated by the steady-state analysis.)

Although the three compartment concept of Riley and Cournand is a parsimonious representation of the inhomogeneous lung, many workers have sought a form of model corresponding more closely to the 'true state of nature' (since in reality the lung corresponds to a continuum of compartments). Thus, many workers have considered the lung as consisting of a number of compartments in parallel (regional inhomogeneity e.g. (254)) whilst others have proposed considering the lung as consisting of a number of compartments in series (stratified inhomogeneity e.g. (260)).

The 'correct' representation has long been an issue of prime contention in the literature.

Intuitively, however, it is felt (on the basis of a conceptual analogy with the case of electric circuits) that every parallel representation will have a series equivalent and hence the above polarisation is unnecessary since one will be unable to differentiate between the competing representations anyway.

Recently, Wagner and Evans (289) have shown, for the specific case of two compartment steady state models, that where series gas exchange occurs, equivalent parallel analysis is also possible. Thus, this tends to support to some extent the above hypothesis.

Most of the inhomogeneous modelling work has focussed on inert gas models (perhaps because the subsequent analysis is simplified for cases which obey Henry's Law). Farhi (98) derived formulae describing the elimination of inert gas in an individual pulmonary unit in the steady state. His analysis showed that the retention (the ratio of concentration in the arterial blood to that in the mixed venous blood) and excretion (the ratio of concentration in expired air to that in mixed venous blood) was dependent only on the ratio of ventilation to perfusion in the pulmonary unit ($\dot{V}$ / $\dot{Q}$) and the solubility of the

inert gas used (λ).

Based on this analysis Farhi and Yokoyama (103, 305) describe a method for determining the $\dot{V}/\dot{Q}$ distribution in a two compartment model using two inert gases and show that in such a technique the solubility of the gases must be carefully chosen.

More recently, again using Farhi's equations (98), Wagner and his associates (292) have described a more ambitious technique for determining the $\dot{V}/\dot{Q}$ distribution in a fifty compartment model using six inert gases with a carefully chosen range of solubilities. From the six values of retention calculated for each inert gas, a non-linear least squares function minimisation method is used to estimate the fractional blood flow in each of the fifty compartments. This method has been used by these workers to investigate the change in $\dot{V}/\dot{Q}$ distribution during 100% O_2 breathing in normal subjects (291) and also to investigate changes in the distribution in subjects with chronic lung disease (290). However, the technique has aroused some criticism in the literature (163, 225, 283, 288) since basically as formulated it constitutes an undetermined mathematical problem. (i.e. since we have 50 parameters and only six measurements the resultant estimates will therefore be non-unique.) Wagner et al (292), although aware of this limitation, in an empirical study of their method were able to accurately recover various artificial distributions and this thus led them to conclude that although there were an infinite number of recoverable solutions they were all in essence very similar. Olszowka (225) has since shown the folly of this claiming Wagner et al (292) were only able to recover the artificial distributions because these coincided with the 'minimal length solutions' (149). In dynamic inhomogenous models it is no longer appropriate to use ventilation-perfusion

ratio ($\dot{V}/\dot{Q}$) as the basic variable underlying gas exchange in a functional pulmonary unit as this is essentially a steady-state concept (255).

In this area most of the models have been developed to quantify inert gas washout tests which have been used as an index of pulmonary function for some years now (119). Therefore, in this situation it is necessary to describe this essentially exponential process via some kind of rate-variable. Although to a control engineer the use of time constant (i.e. time for the process to reach 0.693 of final value) is obvious in this context, in the respiratory physiological literature there has been a prolification of different rate variables. In some work the exponential process is considered as a function of breath number (e.g. rate variables alveolar dilution ratio - see Fowler et al (120), or specific tidal volume - Gomez (132)), whilst in others as a function of time (e.g. rate variables turnover rate - see Robertson et al (247) or half-time Van Liew (286)). However, the work of Rossing (250) has resolved this ambiguity by showing most of these rate variables can be equivalenced if both tidal volume and breathing frequency are constant (which is the usual assumption in most of these analyses). Various forms of distribution function can be used to combine any of the above representations of individual pulmonary units into a description of the overall process taking place in the lung (the units are usually thought of as being in parallel although as discussed earlier, this is merely conceptual).

In the discrete weighting function approach the lung is viewed as consisting of a finite number of compartments (most usually two). Into this category, e.g. falls the work of Fowler et al (120) (2 compartments) and Hashimoto et al (150) (6 compartments). Mention should also be made of the work of Briscoe, Cournand and associates (45) in terms of discrete

compartment analysis. These workers have applied a two compartment representation to the study of diseased lungs in actual subjects (44, 46). Many workers have assumed a continuous distribution function, i.e. viewing the lung as an infinite number of wash-out units.

In mathematical terms, the dependence of the wash-out response $C_{\bar{E}}(t)$ on the distribution function of lung clearance rate variables $G(\lambda)$ can be written in the form

$$C_{\bar{E}}(t) = \int_0^\infty C_A(0)\, G(\lambda)\, e^{-\lambda t}\, d\lambda \qquad 8.1$$

λ being the clearance rate variable for a given functional unit. The aim then is obviously to compute $G(\lambda)$.

To simplify the analysis the distribution function is sometimes assigned a known analytical form, e.g. Rossing et al (251) assume a Gamma distribution which reduces the subsequent estimation problem to finding the three parameters of this distribution.

Nakamura et al (217) have attempted to estimate the distribution function $G(\lambda)$ without recourse to assuming any specific analytical form.

Recognising expression 8.1 as describing a Laplace integral they invert this numerically to obtain $G(\lambda)$ via the Post-Widder equation (236).

This approach has also been used by Okubo et al (224) in a clinical evaluation of the technique applied to differentiate between normal and abnormal function with respect to patients with suspected obstructive lung disease and Lenfant et al (181) in calculating the distribution function of pulmonary blood flow. More recently, however, Peslin (236) has cast doubts on the fundamental numerical aspects of the method.

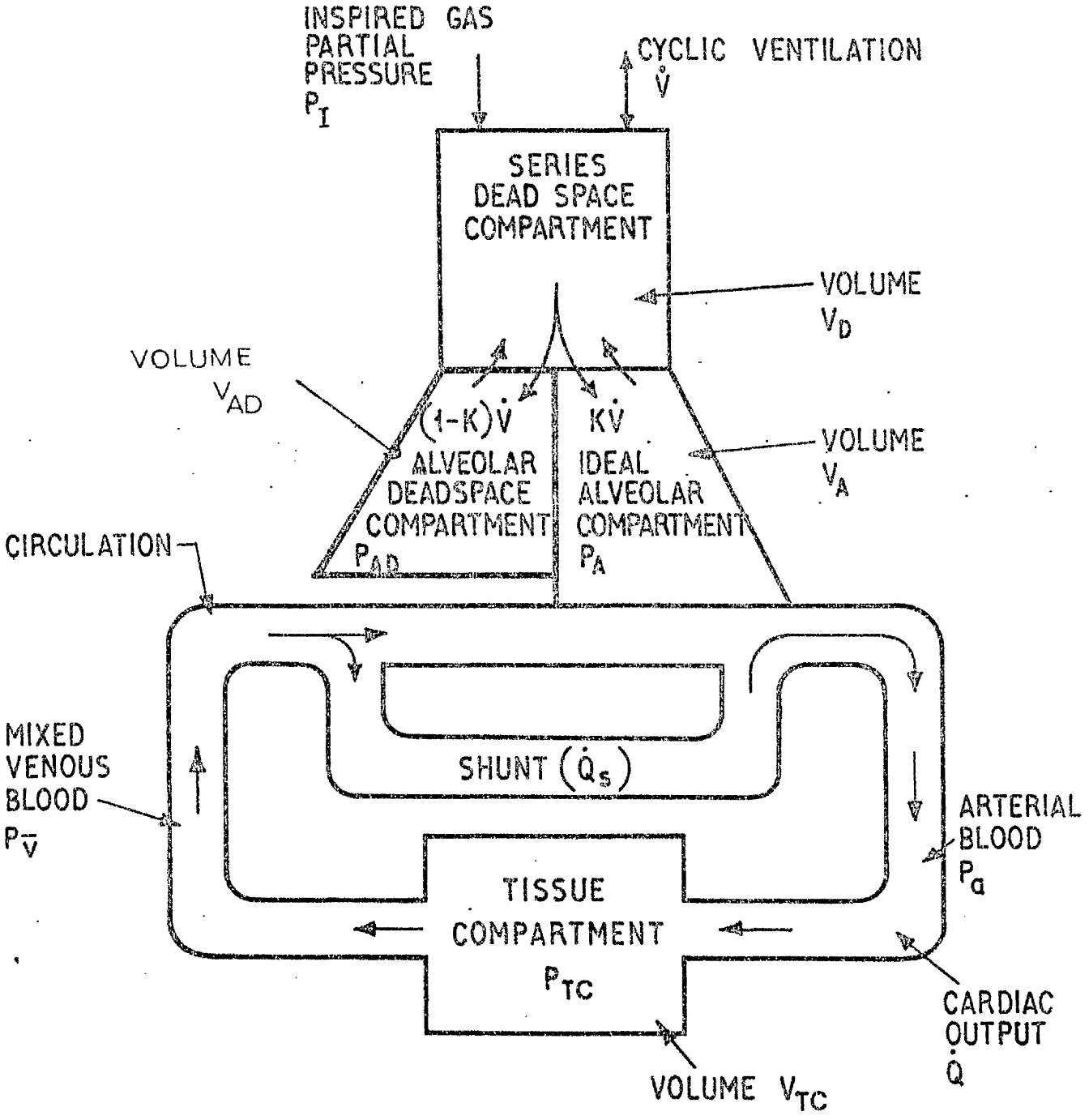
Finally, in a recent new approach Yamashimo et al (304) administered a PRBS input of 100% O_2 and cross-correlated this with the end-expiratory N_2 concentration in order to estimate the impulse response of N_2 clearance. They show the first and second moments of the lung clearance distribution function G (λ) can then be computed by 1st and 2nd. order differentiation of the impulse response function at t = 0. Although apparently open to the same criticisms as the technique of Nakamura et al (217) these authors propose that their technique largely overcomes these problems by working with impulsive as opposed to other forms of output.

8.3 The Dynamic, Inhomogeneous Inert Gas Model

Many of the previous inhomogeneous lung models described in Section 8.2, although more natural in terms of attempting to describe the underlying gas exchange process, are not really suitable for identification purposes due to their inherent redundancy.

Thus, recourse must be made to models which, although more conceptual, functionally describe the essential facets of the process and also allow identification techniques to be applied. This section develops such a model. The identifiability implications of this will be investigated in the succeeding section.

The proposed inhomogeneous model, as mentioned earlier, was inspired by the classical steady state model of Riley and Cournand (246) and is outlined schematically in Fig. 8.2. From this diagram it is seen the structure is basically that of the two compartment homogeneous model described in Chapter 2, but augmented with the addition of an alveolar dead-



INHOMOGENEOUS GAS TRANSPORT MODEL
(INERT GAS)

FIGURE 8·2

space compartment and a right to left shunt ($\dot{Q}_s$) (about which no dynamics are assumed).

Utilising the concepts and quantities of Chapter 2, the system of equations governing this system can be written as follows :

alveolar dead-space compt.

$$V_{A_D} \frac{dP_{A_D}}{dt} = S(1-k)\dot{V}(P_I^* - P_{A_D}) \qquad 8.2$$

'ideal' compt.

$$V_A \frac{dP_A}{dt} = S k \dot{V}(P_I^* - P_{A_D}) + k_1 \dot{Q} \alpha'_{BL}(P_{T_C} - P_A) \qquad 8.3$$

'effective' tissue compt.

$$V_{T_C} \frac{dP_{T_C}}{dt} = \dot{Q} k_1 (P_a - P_{T_C}) \qquad 8.4$$

where V_{A_D} is the volume of the alveolar deadspace compartment, k the fraction of total ventilation distributed to the ideal compartment, and k_1 the fraction of bloodflow distributed to this same compartment (i.e. $\dot{Q}_{total} = k_1 \dot{Q}_{ideal} + (1-k_1)\dot{Q}_s$). α'_{BL} is the Ostwald coefficient between the lungs and blood. As before, V_{T_C} is an effective tissue volume related to the actual physical tissue volume by

$$V_{T_C} = V_{T_C\ actual} \times \frac{\lambda'_{(blood-tissues)}}{\lambda'_{(lungs-blood)}} \qquad 8.5$$

The remaining parameters are analogous to those defined in Chapter 2. From the above equations it is evident the order of the model has been increased by one from that of the homogeneous model.

The assumptions inherent in the model are, where applicable, those made for the cyclic homogeneous model discussed in Chapter 2, (e.g. 'plug-flow' through non-reacting deadspace, no circulatory time delays, etc.). However, several of these assumptions require modification to be applicable to this latest structure. Due to the presence of the 'shunt' we can no longer assume equality of arterial and alveolar partial pressures. The new relationship between these quantities is given by :-

$$P_a = k_1 P_A + (1 - k_1) P_{T_C} \qquad 8.6$$

also, the mean end expiratory partial pressue is modified as follows :-

$$P_{\bar{E}} = \frac{\sum \dot{V}_E [k P_A + (1 - k) P_{A_D}]}{\sum \dot{V}_E} \qquad 8.7$$

where the summations are over the appropriate end-expiratory phase as defined in Chapter 3.

The variations of the ideal and alveolar dead space compartment volumes with time are taken to vary with their respective ventilations as follows :

$$V_A(t) = V_{A(0)} + \int k \dot{V} \, dt \qquad 8.8$$

$$V_{A_D}(t) = V_{A_D(0)} + \int (1 - k) \dot{V} \, dt \qquad 8.9$$

Assumptions also have to be made about the distribution of (series) dead space gas re-inspired; thus again it is assumed dead space gas is distributed to the two alveolar compartments in proportion to their ventilation. If it is assumed gas flows through the dead space with no mixing, then in phase one of the respiratory cycle (see Chapter 2) the gas leaving the dead space and entering the alveolar compartments will be

$$P_D(t) = k P_A (t - \tau) + (1 - k) P_{A_D} (t - \tau) \qquad 8.10$$

where τ is the flow dependent time delay defined as in the case of the homogeneous model by equation 2.32 in Chapter 2. However, due to the fact that the above is difficult to simulate, the dead space partial pressure over phase 1 of the respiratory cycle is taken as the constant value equal to the flow weighted mean from the two alveolar compartments over the last dead space of the previous expiration.

$$P_D = \int_{t_x}^{t_I} \left[\dot{V}_E \, (k P_A + (1 - k) P_{A_D}) \right] dt \qquad 8.11$$

where t_x is given by $\int_{t_x}^{t_I} |\dot{V}_E| \, dt = V_D$ 8.12

The inhomogeneous model as described above has thus six parameters ($\dot{Q}$, V_A, V_T, V_{A_D}, k, k_1) since for inert gases the initial conditions can (unlike in the case for O_2 and CO_2) be safely be assumed a priori to be zero. It remains to investigate in this next section whether this constitutes a unique parameterisation for identification purposes.

8.4 Identifiability of the Inhomogeneous Inert Gas Model

To investigate the identifiability of the inhomogeneous model described in the previous section it is necessary to arrange the equations in state-space format. Defining P_{A_D} as state x_1, P_A as state x_2 and P_{T_C} as state x_3 the state-space matrices (A, B, C, D) based on equations 8.2 to 8.4 are as follows :-

$$A = \begin{bmatrix} a_{11} & 0 & 0 \\ 0 & a_{22} & a_{23} \\ 0 & a_{32} & a_{33} \end{bmatrix} \qquad 8.13$$

The input matrix

$$B = \begin{bmatrix} b_1 \\ b_2 \\ 0 \end{bmatrix} \qquad 8.14$$

for sampling at mouth measurement matrix $C = \begin{bmatrix} c_1 & c_2 & 0 \end{bmatrix}$ 8.15

and $D = 0$ 8.16

where $a_{11} = \dfrac{-(1-k)\dot{V}}{V_{A_D}}$ 8.17

$$a_{22} = \frac{-(k\dot{V} + \lambda'_{BL}\dot{Q})}{V_A} \qquad 8.18$$

$$a_{23} = \frac{\lambda'_{BL} k_1 \dot{Q}}{V_A} \qquad 8.19$$

$$a_{32} = \frac{k_1 \dot{Q}}{V_{T_C}} \qquad 8.20$$

$$a_{33} = \frac{-k_1 \dot{Q}}{V_{T_C}} \qquad 8.21$$

$b_1 = (1-k)\dot{V}$ - 8.22 ; $b_2 = k\dot{V}$ - 8.23

$c_1 = (1 - k_1)$ - 8.24 ; $c_2 = k_1$ - 8.25

as in previous identifiability studies on gas exchange models (c.f. Chapter 4) we assume constant ventilation, i.e. $\dot{V}$ = const.

Recall from state space theory the transfer function of this system is obtained from the matrices (A, B, C, D) as follows :-

$$G(S) = C\left[S I - A \right]^{-1} B = C \frac{\text{adj}\,(S I - A)}{\det (S I - A)} B = \frac{N(S)}{D(S)} \qquad 8.26$$

Due to the arithmetic complexity there are advantages in calculating adj (SI - A) and det (SI - A) in terms of the state space parameters (a_{11} , a_{22} etc.) rather than the intrinsic model parameters ($\dot{Q}$, V_A, V_{A_D} etc.). If this is done, after some arithmetic labour we obtain the following expressions for N(S) and D(S).

$$N(S) = \alpha_1 S^2 + \alpha_2 S + \alpha_3 \qquad 8.27$$

$$D(S) = S^3 + \alpha_4 S^2 + \alpha_5 S + \alpha_6 \qquad 8.28$$

where α_1 , ... α_6 are given by

$$\alpha_1 = c_1 b_1 + c_2 b_2 \qquad 8.29$$

$$\alpha_2 = - c_1 b_1 (a_{22} + a_{33}) + c_2 b_2 (a_{11} + a_{33}) \qquad 8.30$$

$$\alpha_3 = c_1 b_1 (a_{22} a_{33} - a_{23} a_{32}) + c_2 b_2 a_{11} a_{33} \qquad 8.31$$

$$\alpha_4 = - (a_{11} + a_{22} + a_{33}) \qquad 8.32$$

$$\alpha_5 = (a_{11} a_{22} + a_{11} a_{33} + a_{22} a_{33} - a_{23} a_{32}) \qquad 8.33$$

$$\alpha_6 = - a_{11} (a_{22} a_{33} - a_{23} a_{32}) \qquad 8.34$$

Notice from the above equations that the parameterisation in terms of the state space parameters is not unique since there are 9 state space parameters and only 6 independent Laplace transform coefficients. However, by aggregating the parameters

c_1 , b_1, c_2, b_2, a_{23} and a_{32} as follows — :

$$c_1 b_1 = a \qquad 8.35$$

$$c_2 b_2 = b \qquad 8.36$$

$$a_{23} a_{32} = c \qquad 8.37$$

we achieve a unique solution in terms of this parameterisation. This is an example of how this sort of analysis can be useful in eliminating redundancy in this form of compartmental model. Equations 8.29 - 8.34 can be written in terms of the intrinsic model parameters as follows :-

$$\alpha_1 = (1-k)^2 \dot{V} + k^2 \dot{V} \qquad 8.38$$

$$\alpha_2 = (1-k)^2 \dot{V}\left[\frac{k\dot{V}}{V_A} + \frac{\lambda'_{BL} k_1 \dot{Q}}{V_A} + \frac{k_1 \dot{Q}}{V_{T_C}}\right] + k^2 \dot{V}\left[\frac{(1-k)\dot{V}}{V_{A_D}} + \frac{k_1 \dot{Q}}{V_{T_C}}\right] \qquad 8.39$$

$$\alpha_3 = (1-k)^2 \dot{V}\left[\frac{k\dot{V} k_1 \dot{Q}}{V_A V_{T_C}}\right] + k^2 \dot{V}\left[\frac{(1-k)\dot{V} k_1 \dot{Q}}{V_{A_D} V_{T_C}}\right] \qquad 8.40$$

$$\alpha_4 = \frac{(1-k)\dot{V}}{V_{A_D}} + \frac{k\dot{V}}{V_A} + \frac{B k_1 \dot{Q}}{V_A} + \frac{k_1 \dot{Q}}{V_{T_C}} \qquad 8.41$$

$$\alpha_5 = \frac{k\dot{V}}{V_A}\left[\frac{k_1 \dot{Q}}{V_{T_C}}\right] \qquad 8.42$$

$$\alpha_6 = \frac{(1-k)\dot{V}}{V_{A_D}}\left[\frac{k\dot{V}}{V_A}\left(\frac{k_1 \dot{Q}}{V_{T_C}}\right)\right] \qquad 8.43$$

It might appear at first sight that the model parameterisation could be assumed unique since we have six model parameters and six equations. However, closer scrutiny of the equations above reveals the parameters k_1 and $\dot{Q}$ to be unidentifiable (i.e. only the product $k_1 \dot{Q}$ can be uniquely estimated). Physically this means that neither the degree of shunt nor the cardiac output can be identified from measurements at the mouth using this model, but only the product $k_1 \dot{Q} = \dot{Q}^*$ which conceptually could be thought of as a sort of 'effective pulmonary blood flow' flowing through the 'ideal' alveolar compartment. It is pertinent to enquire if the shunt and total cardiac output can be decoupled under any circumstances. If it was possible

to sample arterial gas tensions another transfer function could be obtained relating this quantity to the inspired gas partial pressure. This is obtained by substituting a different measurement matrix C' into equation 8.26 to obtain a different G(S). This measurement matrix is given by

$$C' = \begin{bmatrix} 0 & c_3 & c_4 \end{bmatrix} \qquad 8.44$$

where

$$c_3 = k_1 \qquad 8.45$$

$$c_4 = (1 - k_1) \qquad 8.46$$

are obtained from consideration of equation 8.6 earlier. If this is done although the denominator of the resultant transfer function is the same as that for sampling at the mouth earlier we obtain a different numerator N (S) given by

$$N(S) = \alpha_7 S^2 + \alpha_8 S + \alpha_9 \qquad 8.47$$

where in terms of the state space parameters we have

$$\alpha_7 = c_3 b_2 \qquad 8.48$$

$$\alpha_8 = c_4 b_2 a_{32} - (a_{11} + a_{33}) \qquad 8.49$$

$$\alpha_9 = c_3 b_2 a_{11} a_{33} - a_{11} c_4 b_2 a_{32} \qquad 8.50$$

Arterial sampling thus contributes three more independent equations to the system to be solved in addition to the six given earlier, in terms of the intrinsic model parameters these become

$$k_1 k \dot{V} = \alpha_7 \qquad 8.51$$

$$(1 - k_1) k \frac{\dot{V} k_1}{V_{T_C}} \dot{Q} + \frac{(1 - k) \dot{V}}{V_{A_D}} + \frac{k_1 \dot{Q}}{V_{T_C}} = \alpha_8 \qquad 8.52$$

$$k_1 k \dot{V} \frac{(1 - k) \dot{V}}{V_{A_D}} \frac{\lambda'_{BL} \dot{Q}}{V_{T_C}} + (1 - k_1) \frac{k \dot{V}}{V_{A_D}} \frac{k_1 \dot{Q}}{V_{T_C}} = \alpha_9 \qquad 8.53$$

Inspection of these extra equations shows if they can be made available they can thus allow us to decouple the parameters k_1 and $\dot{Q}$. Unfortunately, at the present moment in time, continuous measurement of P_a is beyond the state of the art as far as mass spectrometry is concerned. Thus, disappointingly we will be unable to use this model to decouple shunt and cardiac output until this measurement becomes available, i.e. this leaves us with a five per model with $k_1 \dot{Q}$ reparamaterised as $\dot{Q}^* = k_1 \dot{Q}$. Having investigated the structural identifiability of the model, it is now appropriate to explore the degree of identifiability of the model. This has been done using a simulation programme (LUNG 4) analagous to those described for the homogeneous model in earlier chapters which assumes sinusoidal ventilation.

The inhomogeneous model (assuming an inert gas with solubility $\lambda'_{BL} = 2.0$) was driven by a square wave stimulus. Parameter values and experimental conditions used were :

homogeneous model $\dot{Q} = 5$ L/M; $V_A = 3$ L ; $V_{T_C} = 7.5$ L ;

inhomogeneous model $\dot{Q} = 5$ L/M ; $V_A = 1.5$L; $V_{A_D} = 1.5$L ; $k = 0.5$; $V_{T_C} = 7.5$ L.

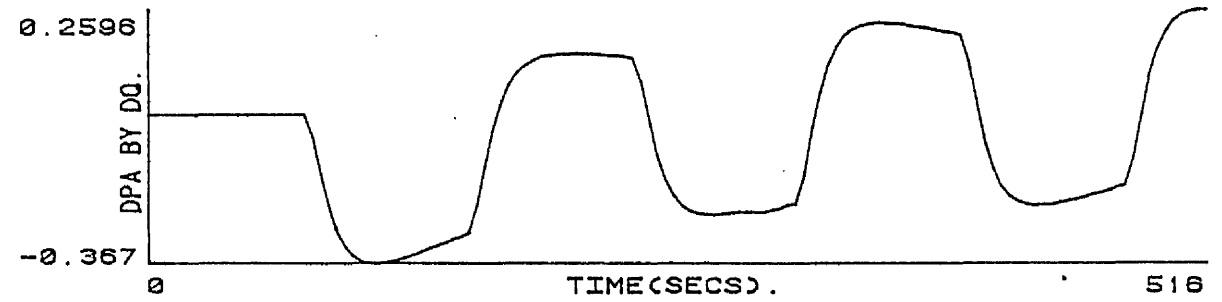
experimental conditions were :-

$\dot{V} = 8$ L/M; $V_D = 0.2$ L; breathing freq. = 15 br/min :

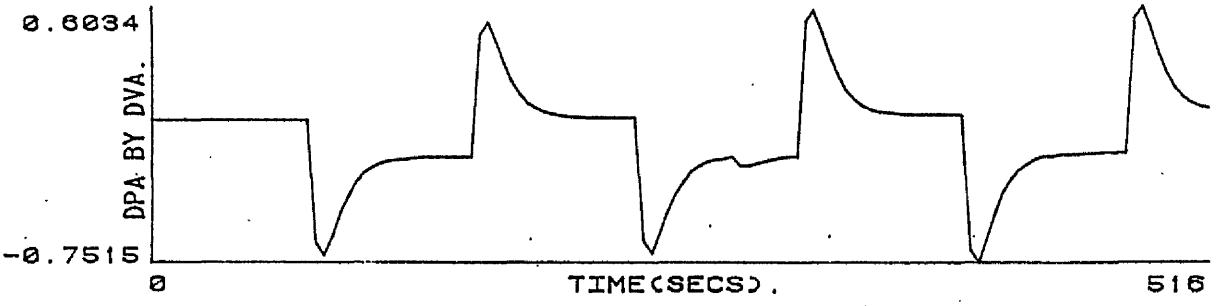
no. of breaths = 130 ; C_I (%) = 7% ; $\tau/2 = 20$ breaths.

The sensitivity functions corresponding to this input are shown in Fig. 8.3. Sensitivities to $\dot{Q}$, V_A , V_{T_C} are similar to those of the homogeneous model. It was found variation of the sensitivity function for flow fraction k was highly dependent on the value of k used ; much more so than the other

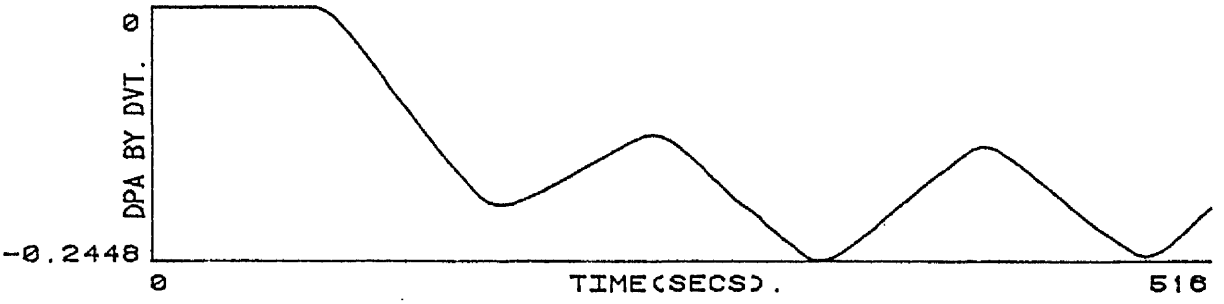
INHOMOGENEOUS MODEL-SENSITIVITY FNS (N=5).



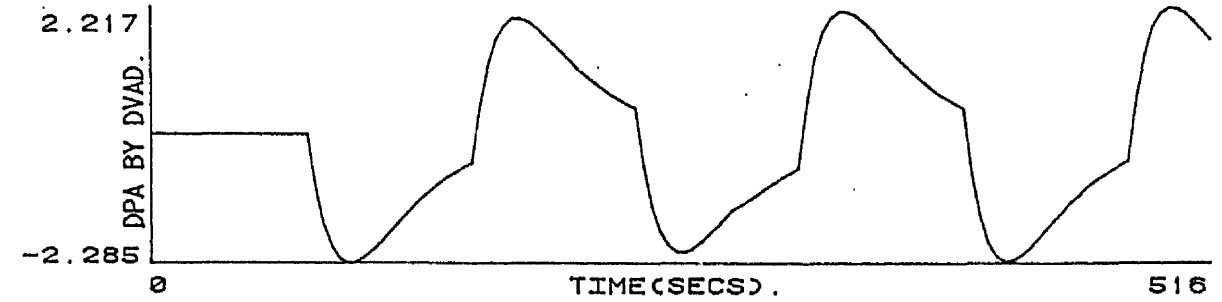
SENSITIVITY TO PULMONARY BLOOD FLOW.



SENSITIVITY TO LUNG VOLUME.



SENSITIVITY TO TISSUE VOLUME.



SENSITIVITY TO ALVEOLAR DEADSPACE VOLUME.

SENSITIVITY TO FLOW FRACTION.

FIGURE 8·3

sensitivities. This is illustrated in Figure 8.4.

Extensive simulation studies of this five parameter inhomogeneous gas exchange model were conducted. From these it became apparent that although the model was identifiable problems of determinancy (in the sense defined by Brown and Godfrey (44)) existed. For different sets of parameter values and simulated experimental conditions large correlations between various parameters were a frequent occurrence (often, but not always between k, V_A , V_{A_D}) and the condition number of $X^T X$ (X being the sensitivity matrix) was consistently large, i.e. for the experiment and paramater values given above.

$$\frac{\lambda_{max}}{\lambda_{min}} (X^T X) = 5.3 \times 10^4 \qquad 8.54$$

Thus, on the basis of these observations it was decided to attempt to reduce the ill-conditioned nature of the model by attempting to find some relationship between the parameters which allows us to reduce their number ; the object behind this to make the model a better proposition for subsequent identification studies.

One way in which this can be done is to assume ventilation is distributed to the two alveolar compartments in proportion to their respective volumes, i.e.

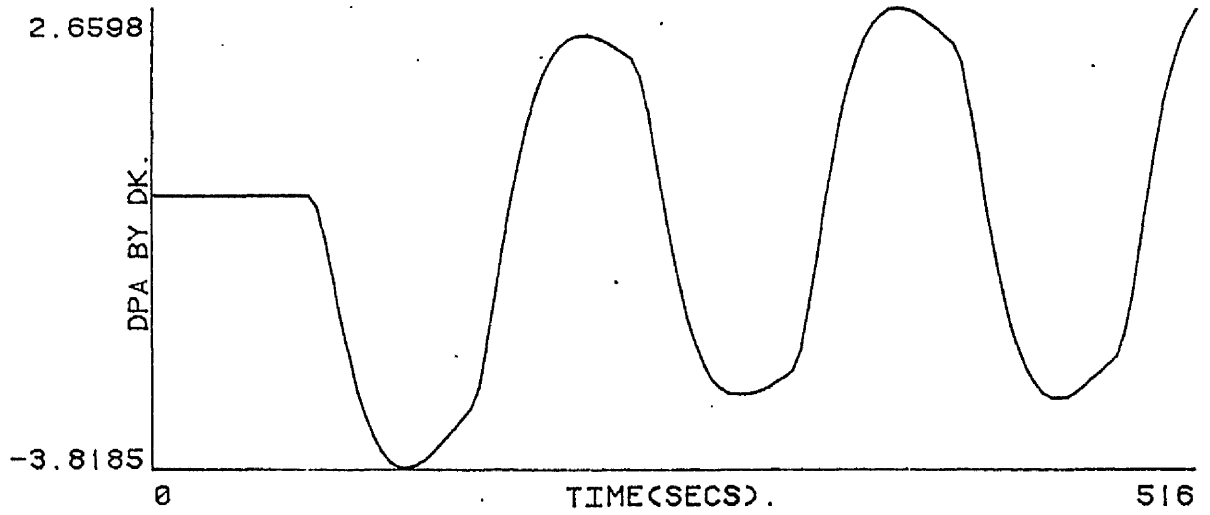
$$\frac{V_A}{V_{A_D}} = \frac{k}{(1-k)} \qquad 8.55$$

This allows reparamaterisation of k (and (1-k)) in terms of V_A and V_{A_D} e.g.

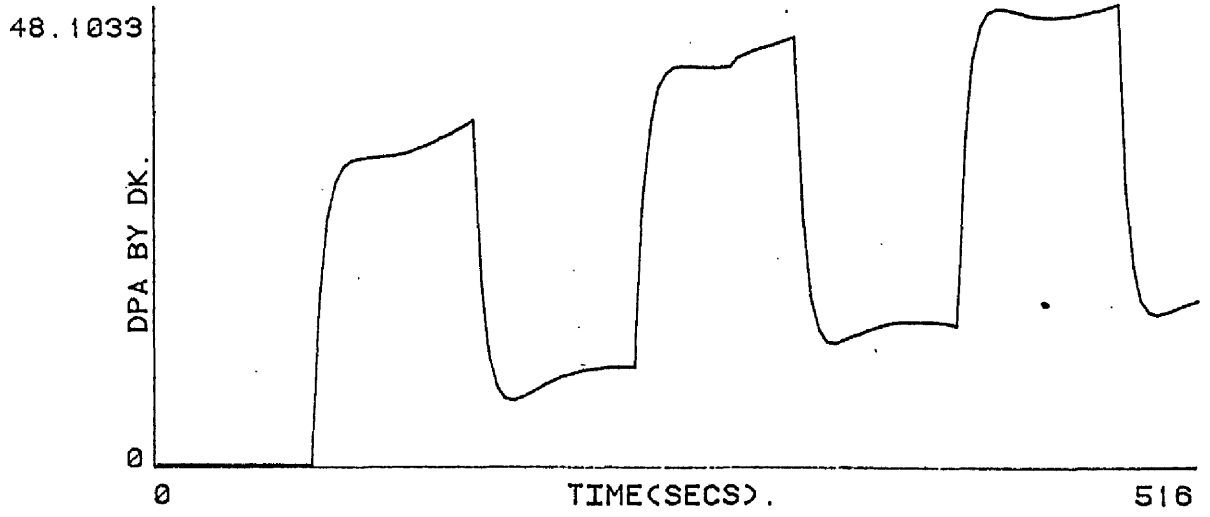
$$k = \frac{V_A}{(V_A + V_{A_D})} \qquad 8.56$$

VARIATION OF DPA BY DK WITH FLOW FRACTION.

FLOW FRACTION = 0.25.



FLOW FRACTION = 0.5.



FLOW FRACTION = 0.8.

FIGURE 8·4

The number of parameters β in the model is thus reduced from five to four by this mechamism. ($\beta = (\dot{Q}^{*}, V_A, V_T, V_{A_D})^T$). The above assumption is not altogether unreasonable physiologically and in fact has frequently been made by other workers in this area (150). With this re-paramaterisation the set of non-linear equations (equations 8.38 - 8.43) defining the relationship between the coefficients of the model input/output transfer function and its intrinsic parameters become :

$$\frac{\left[V_{A_D}^{2} = V_A^{2} \right]}{(V_A + V_{A_D})^2} = \alpha_1 \qquad 8.57$$

$$\dot{V}^2 \frac{\left[V_{A_D}^{2} + V_A^{2}\right]}{(V_A + V_{A_D})^3} + \frac{Q^{*}\dot{V}}{V_{T_C}} \frac{\left[V_{A_D}^{2} + V_A^{2}\right]}{(V_A + V_{A_D})^2} + \frac{V_A^{2}\,\dot{V}\,\dot{Q}^{*}}{V_{T_C}(V_A + V_{A_D})^2} = \alpha_2 \qquad 8.58$$

$$\frac{\dot{Q}^{*}\dot{V}^2}{(V_A + V_{A_D})^2} \cdot \frac{\left[V_{A_D}^{2} + V_A^{2}\right]}{V_{T_C}} = \alpha_3 \qquad 8.59$$

$$\left(\frac{2\dot{V}}{V_A + V_{A_D}}\right) + \frac{\lambda'_{BL}\dot{Q}^{*}}{V_A} + \frac{\dot{Q}^{*}}{V_{T_C}} = \alpha_4 \qquad 8.60$$

$$\frac{\dot{V}^2}{(V_A + V_{A_D})^2} + \frac{2\dot{V}\dot{Q}^{*}}{V_{T_C}(V_A + V_{A_D})} + \frac{\dot{V}\lambda'_{BL}\dot{Q}^{*}}{V_A(V_A + V_{A_D})} = \alpha_5 \qquad 8.61$$

$$\frac{\dot{V}^2}{(V_A + V_{A_D})^2} \cdot \frac{\dot{Q}^{*}}{V_{T_C}} = \alpha_6 \qquad 8.62$$

From consideration of these equations it does not appear as if the structural identifiability is untowardly affected by the introduction of the modified model

paramterisation. The new parameterisation, however, does explicitly change, as would be expected, the form of the sensitivity functions for V_A and V_{A_D} although the effect on the other sensitivity functions is minimal. These are shown in Figure 8.5. The variation of the sensitivities functions for V_A and V_{A_D} with distribution of ventilation to the two alveolar compartments (i.e. with partitioning of a total conceptual lung volume between V_A and V_{A_D} .) is shown in Figures 8.6 and 8.7. This shows the great dependence of these senstivity functions on a priori paramater values. By reducing the number of parameters from five to four in the model, it was found the ill-conditioned nature of the sensitivity matrix was markedly reduced, i.e. for the equivalent conditions defined for the five parameter model above the condition number of $X^T X$ for the four parameter model was

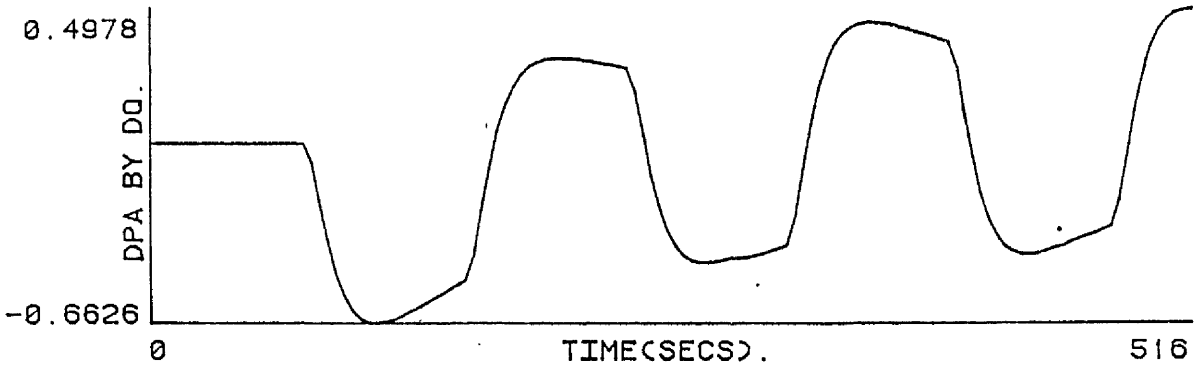
$$\frac{\lambda_{max}}{\lambda_{min}} (X^T X) = 1.3 \times 10^4 \qquad 8.63$$

Thus the condition number is reduced by a factor of greater than ten by postulating this new model structure. Functionally, therefore, provided the assumptions are reasonable, this latter model represents a better candidate for identification.

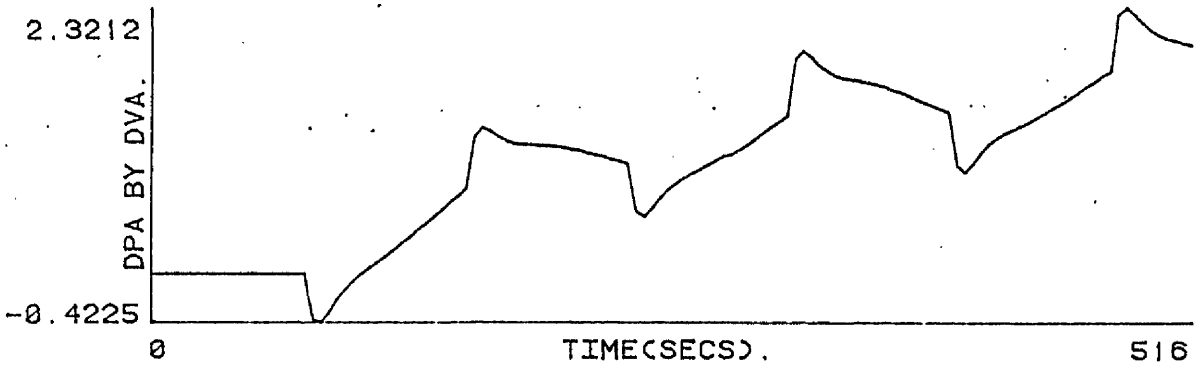
8.5 Experiment Design for Structure Discrimination - Theory

In the introductory section of this chapter it was mentioned that the inhomogeneous gas transport model was to be used in a technique to distinguish between normal and abnormal pulmonary function at a clinically useful stage. Central to this is the concept of designing identification

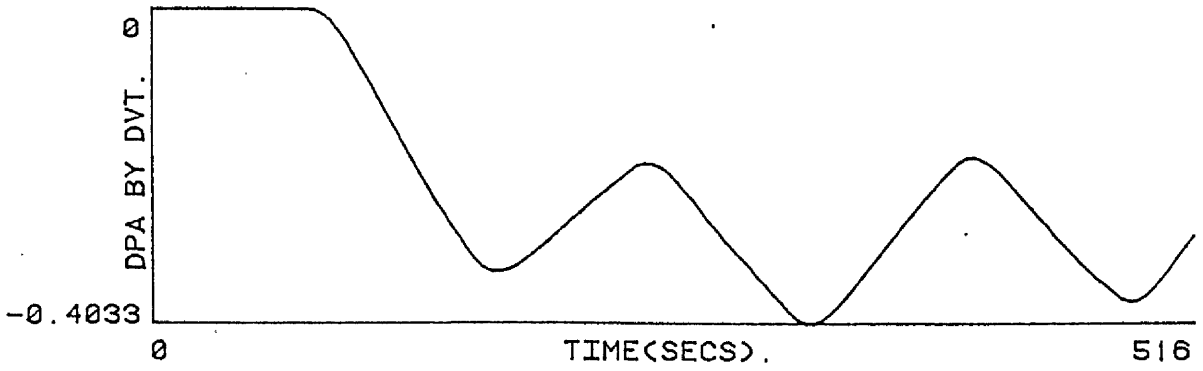
INHOMOGENEOUS MODEL-SENSITIVITY FNS (N=4).



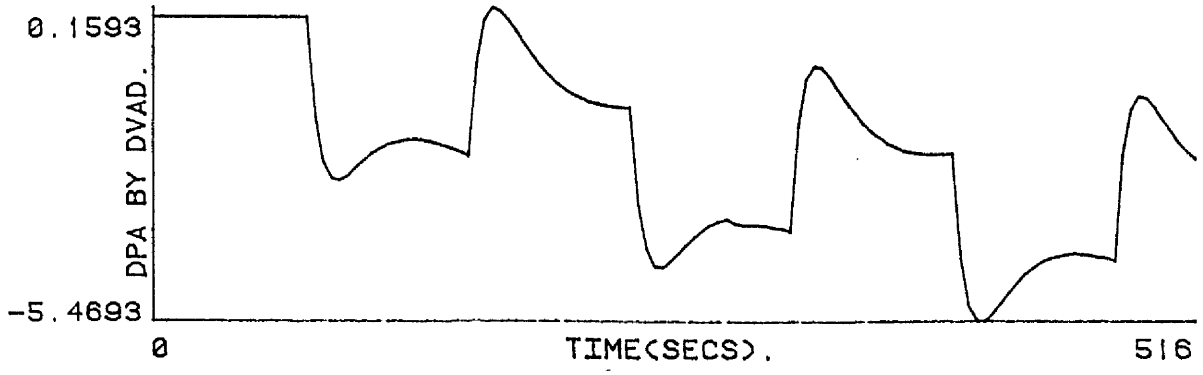
SENSITIVITY TO PULMONARY BLOOD FLOW.



SENSITIVITY TO LUNG VOLUME.



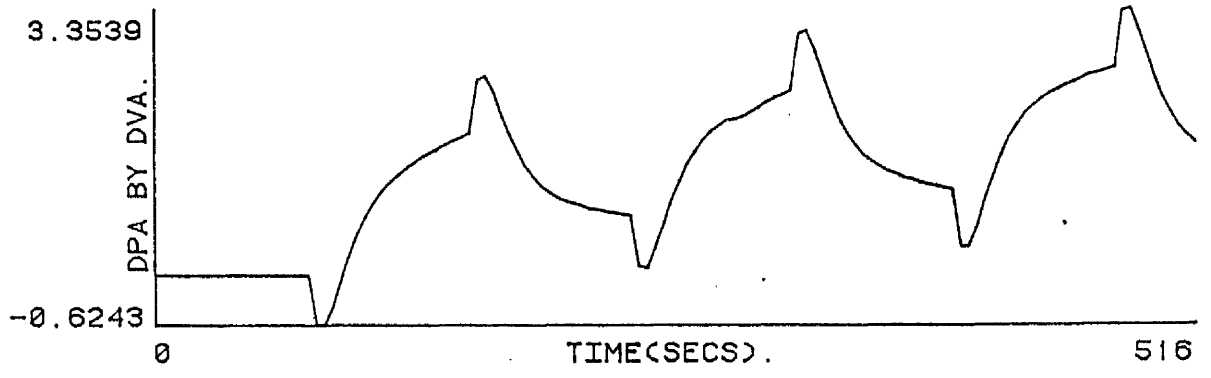
SENSITIVITY TO TISSUE VOLUME.



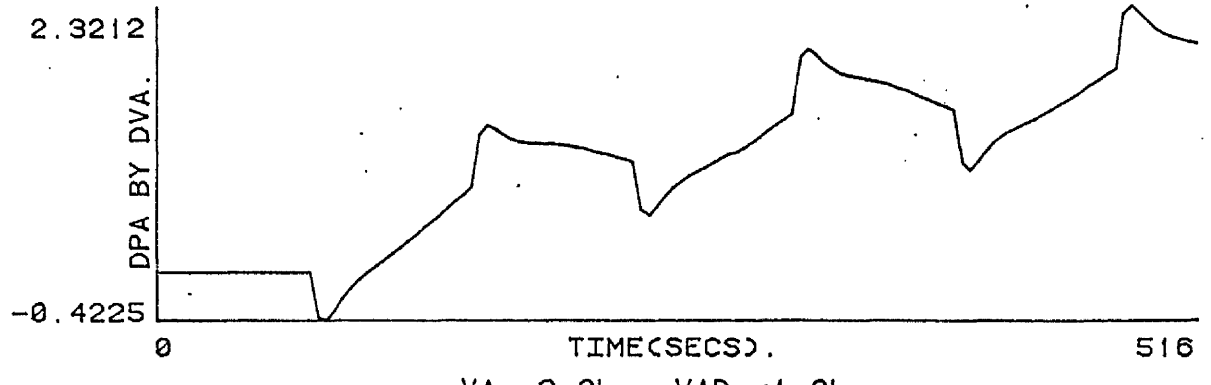
SENSITIVITY TO ALVEOLAR DEADSPACE VOLUME.

FIGURE 8·5

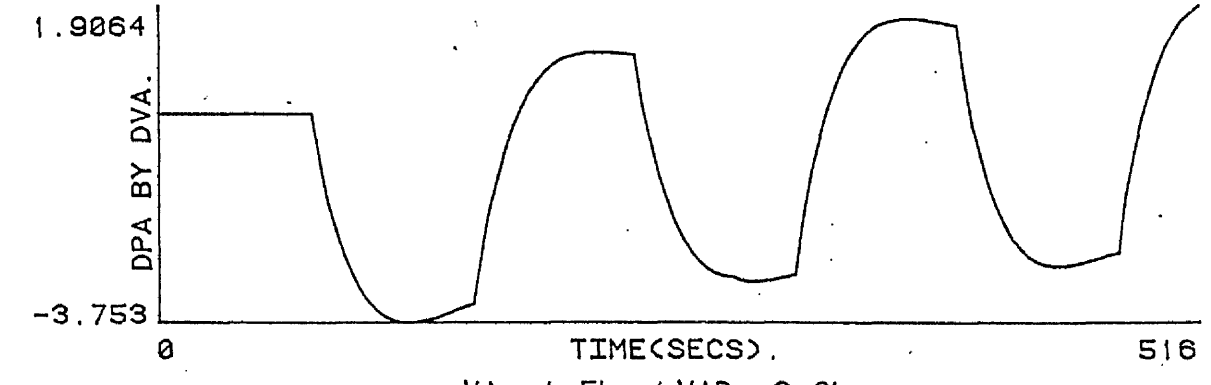
DPA BY DVA VARIATION WITH FLOW DISTRIBUTION.



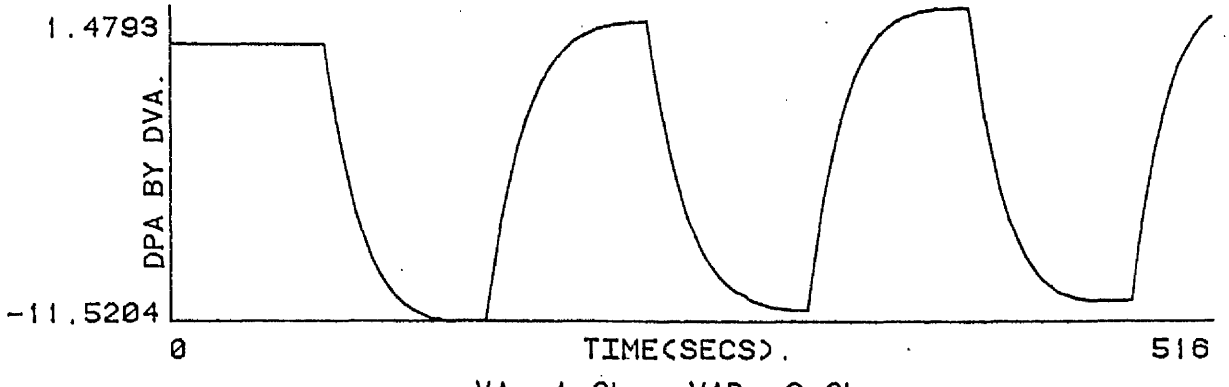
VA =2.5L ; VAD =0.5L .



VA =2.0L ; VAD =1.0L .



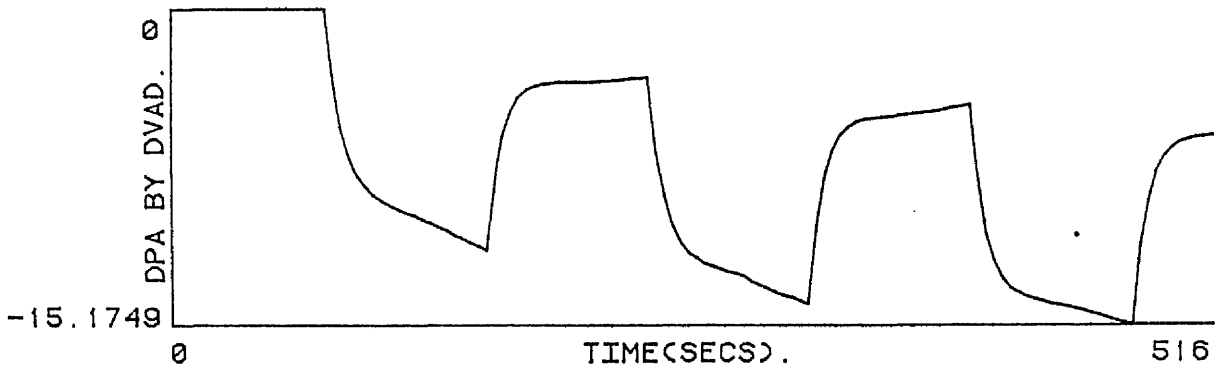
VA =1.5L ; VAD =2.0L .



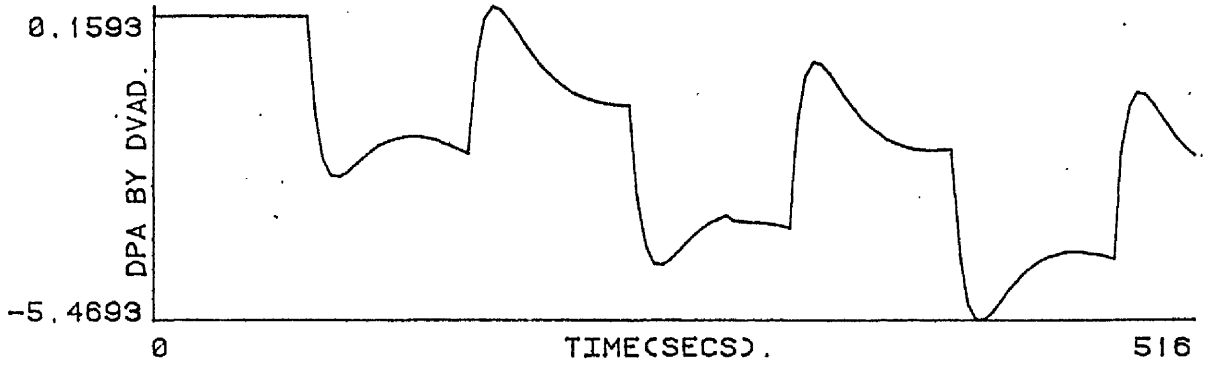
VA =1.0L ; VAD =2.0L .

FIGURE 8·6

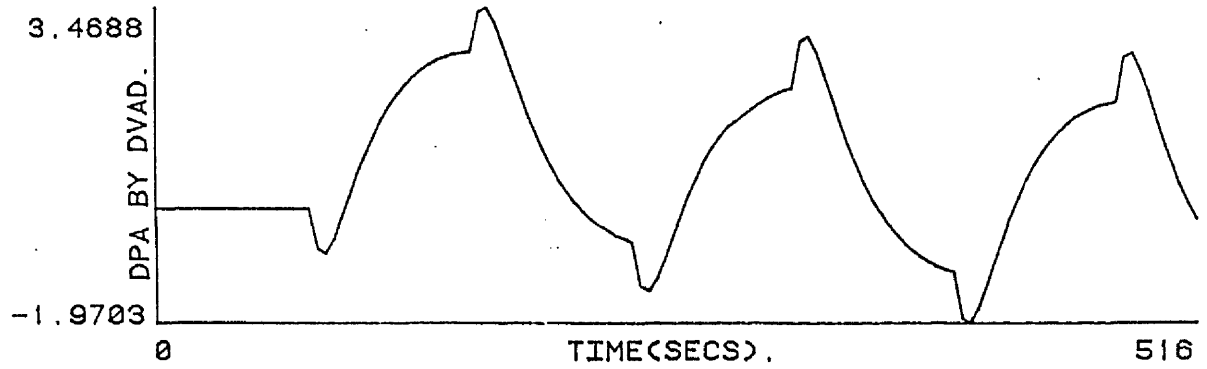
DPA BY DVAD VARIATION WITH FLOW DISTRIBUTN.



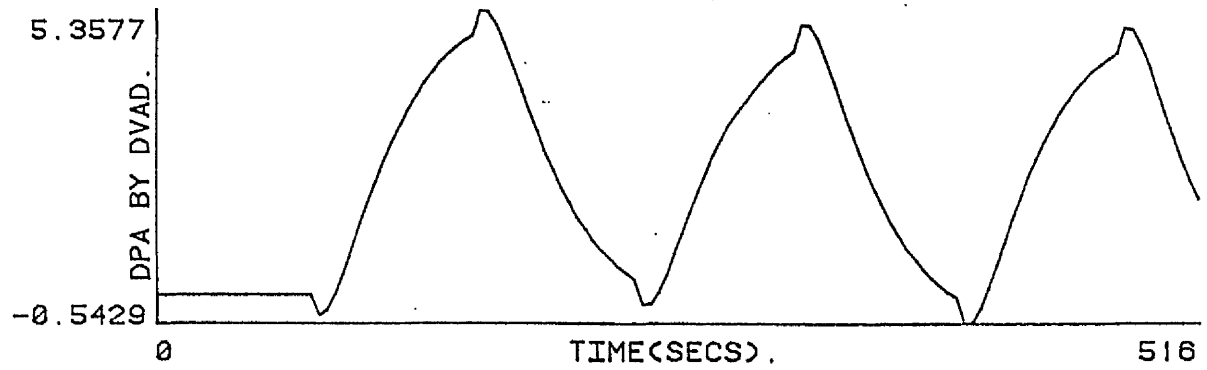
VA = 2.5L ; VAD =0.5L .



VA = 2.0L ; VAD =1.0L .



VA =1.5L ; VAD =1.5L .



VA =1.0L ; VAD =2.0L .

FIGURE 87

experiments to optimally discriminate in the presence of noise between the homogeneous and inhomogeneous gas exchange models ; both of which are competing to describe the underlying data generating mechanism in any given patient. Having designed the identification experiment it is envisaged some appropriate test of model structure is used to decide the appropriate model. Such techniques may for example be those described in Chapter 4, or the likelihood ratio test to be subsequently described.

The design of experiments for discriminating among alternative model structures can be viewed as an extension of the methods discussed in Chapter 7 concerned with the design of experiments for accurate parameter estimation within a model of specified structure. The structure discrimination problem is still in fact an active research area (predominantly in the statistical literature (4, 17, 18, 105))and no unified theory yet exists . Correspondingly reported applications are sparse with the work of Swanson (275) in the respiratory control modelling area and Koopmans (178) who discusses the problem in relation to economic systems, being exceptions.

Theoretically, the largest barrier to progress lies in difficulty in defining a meaningful criterion. A number of different criteria have been proposed.

Lindley and Smith (186) presented a criterion based on Bayesian principles. Box and Hill (38) proposed an information- theoretical approach where the structural design problem is treated analogously to that of signal discrimination in communication theory. In Beck and Arnold, Chapter 8 (22), a deterministic approach to the problem is outlined. They derive different criteria from sensitivity principles dependent on which competing model, if any, is assumed a priori to be correct. As is shown by Atkinson (16), under certain conditions such criteria can be given statistical interpretations.

In the context of the present study we shall adopt a hypothesis testing approach. As we shall see, such a formulation has, for our purposes, certain advantages and leads to the derivation of a criterion with a more satisfactory basis. The approach is basically that of Kabaila (166) as described in (137). However, before developing the proposed discrimination criterion it is necessary to review briefly the classical Neyman-Pearson theory of hypothesis testing (218).

This theory is concerned -with two hypotheses; the first called the null hypothesis Ho, which is that of primary interest and the second the complement of Ho which is termed the alternative hypothesis HA. A statistical test of Ho against the alternative HA partitions the sample space into a region of acceptance of Ho denoted by the set S and its complementary region, a region of rejection of Ho which we will denote by $\bar{S}$. The latter is usually known as the critical region.

In such a test we could commit two types of errors.

Type **I** - Reject H_o when it is in fact true - the probability of this is given by α = prob ($\bar{S}$ / Ho).

Type II - Accept Ho when it is in fact false - the probability of this being β = prob (S / HA) = 1 - prob ($\bar{S}$ / HA).

The quantity α is called the significance level of the test and $1 - \beta$ the power function of the test.

A test whose error probabilities α and β are as small as possible is clearly desirable. However, equally clearly we cannot chose $\bar{S}$ in such a way that each of these probabilities is simultaneously minimised. This conflict is resolved by recognising in that many circumstances our attitude to the hypotheses Ho and HA are different. We are often concerned with the question as to whether there is sufficient evidence to reject Ho.

In this respect a Type I error may be looked upon as more important than a Type II. This was explicitly recognised by Neyman and Pearson who proposed we should control the probability of a Type I error (i.e. fix α) then look for a test for which a Type II error is minimised, (i.e. the power function ($1 - \beta$) is maximised). A test with useful properties in this respect is the Likelihood Ratio test (261, Ch. 6 / 7 .) given as follows. Suppose the observations come from one of a (broad) class of distributions and we want to test the hypothesis Ho that they come from a distribution belonging to a particular sub-class. To test this using the Likelihood Ratio test we form the Likelihood ratio λ (y) by using as the numerator the maximum of Likelihood over the broad class and as the denominator the maximum of the Likelihood over the sub-class. Let ϕ be the parameterisation of the general distribution and let ϕ_0 be the M.L.E. under Ho and ϕ_1 the M.L.E. under HA respectively.

$$\lambda\,(y) = \frac{\max \text{ prob}\,(y/\phi_1)}{\max \text{ prob}\,(y/\phi_0)} \qquad 8.64$$

Clearly the smaller ratio, the less inclined we are to accept the null hypothesis Ho on the basis of the given data. The decision rule will be : reject Ho if $\lambda > \lambda_\alpha$ where λ_α is determined so that

$$\text{prob}\,(\lambda > \lambda_\alpha / \text{Ho}) = \alpha \qquad 8.65$$

α being the significance level of the test. However, what of the probability distribution of λ ? Say the data consists of identical, independently distributed observations and the null hypothesis is that there are 'r' locally independent restrictions of the form —:

$$\beta_1 - \beta_1^* = 0 \qquad 8.66$$

between the first 'r' parameters (β_1) of the more general distribution parameterisation (ϕ) , i.e. β_1^* is a fixed length vector and β_1 is given by

$$\phi = \begin{bmatrix} \phi_1 \\ \phi_2 \\ \cdot \\ \cdot \\ \phi_r \\ --- \\ \phi_{r+1} \\ \cdot \\ \cdot \\ \phi_n \end{bmatrix} = \begin{bmatrix} \beta_1 \\ \\ ---- \\ \\ \beta_2 \end{bmatrix} \qquad 8.67$$

Under these assumptions it can be shown (261, Ch. 7) that 2 log λ (y) is distributed according to a χ^2 distribution on 'r' degrees of freedom, i.e. 2 log λ (y) converges in law (or probabilistically) to χ (r). In this situation the decision procedure given by equation 8.65 reduces to comparing 2 log λ (y) with the value k_α obtained from the cumulative χ^2 (r) distribution (k_α being such that 100 α % of the distribution lies to the right of k_α). We reject Ho if 2 log λ (y) > k_α .

Thus far we have been concerned only with the significance level of the Likelihood Ratio test. To investigate the power of the test it is necessary to consider what happens to the probability distribution of 2 log (λ (y)) under a specific alternative hypothesis HA, e.g. that the 'true' value of β_1 is β_A not β^* .

Under this hypothesis (with the same conditions prevailing as in the discussion above) it transpires that 2 log λ (y) is distributed according to a non-central χ^2 distribution on 'r' degrees of freedom, i.e. 2 log λ (y) converges in law to χ'^2 (s, h) , with the non-centrality parameter h given by

$$h = (\beta_A - \beta^*)^T \left[M_{\beta_1\beta_1} - M_{\beta_1\beta_2} M^{-1}_{\beta_2\beta_2} \right] (\beta_A - \beta^*)^T \qquad 8.68$$

$\chi^a(s,h)$ can be approximated for h large by a normal distribution with mean h and variance 4 h whilst the $\chi^2(r)$ distribution can be asymtotically approximated as a sum of squares of 'r' independent zero mean, unit variance normal variables. The probability density functions for $2 \log \lambda(y)$ under both Ho and HA are shown in Figure 8.8

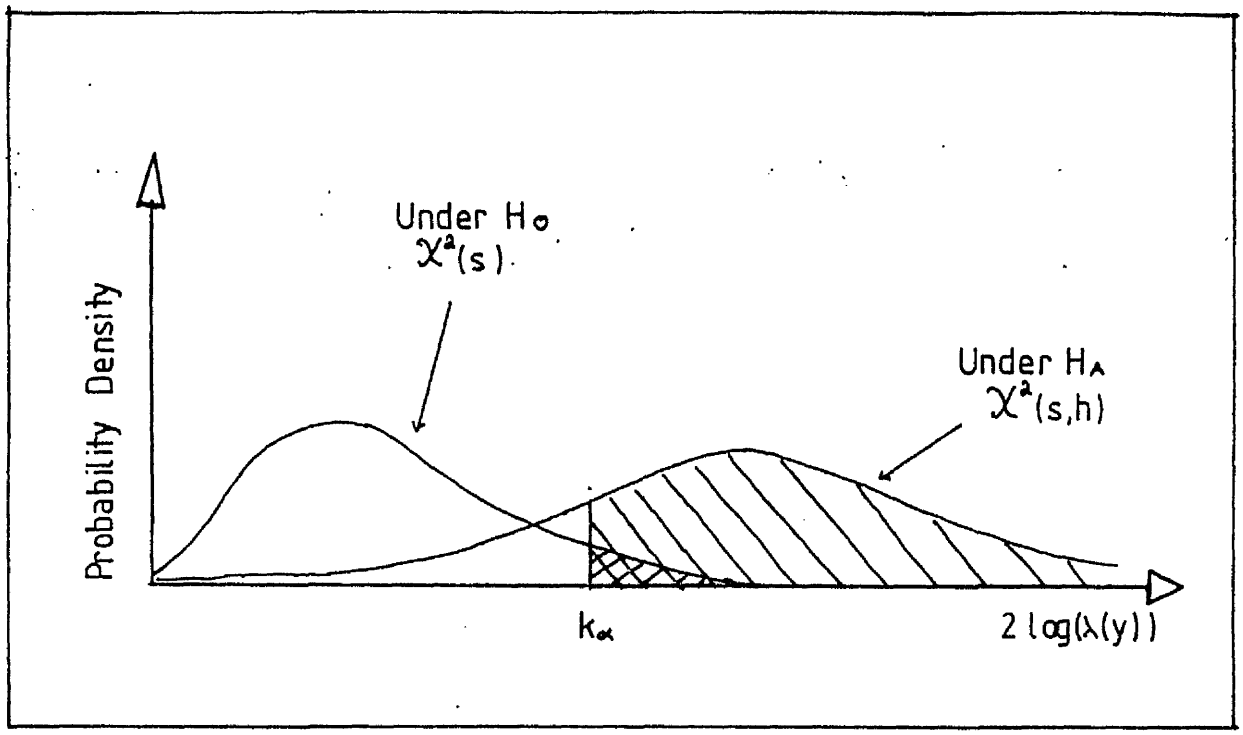
Notice that the area of the $\chi^2(r)$ to the left of k_α corresponds to the significance level of the test and that of the $\chi'^2(r, h)$ to the left of k_α to the power of the test. Thus from this diagram we reach the conclusion that (for a fixed significance level α) the power of the test is related to the non-centrality parameter h, i.e. the power of the test is increased by making h large. This therefore allows us to make the important connection between the 'goodness' of a structure discrimination test and the form of experiment used since h is a function of the information matrix M and hence of the experiment design.

Having justified the concept of maximising the power of the test via h, different experimental design criteria can be suggested based on this. For example, a locally optimum criterion which maximises h for a specific β_A (so called T - optimum criterion) or a minimax criterion, both of which are discussed by Atkinson and Federov (18). However, perhaps the most useful is the D_s - optimal criterion (137, Ch. 6) which is given by

$$J_s = \det \left[M_{\beta_1\beta_2} - M_{\beta_1\beta_2} M^{-1}_{\beta_2\beta_2} M_{\beta_1\beta_2} \right] \qquad 8.69$$

$$= \det \left[M_{\beta\beta} \right] / \det \left[M_{\beta_2\beta_2} \right]$$

PROBABILITY DISTRIBUTION FOR 2 LOG(λ(y))



/// area = significance level of test.

\\\ power of test.

FIGURE 8·8

Analagous to the D optimal and truncated D optimal design criteria for accurate parameter estimation discussed in Chapter 7, this criterion is invariant of scale changes in the parameters. Also in our application it has advantages over the T optimum criterion in requiring less a priori information (i.e. the value of β_A against which it is desired to discriminate; this is generally unknown initially). Thus in the next section the D_s optimal criterion will be utilised in the context of gas exchange modelling to investigate various structure discrimination experiments for differentiation between homogeneous and inhomogeneous models.

8.6 Experiment Design for Structure Discrimination Between the Homogeneous and Inhomogeneous Inert Gas Models

This section is concerned with the design of identification experiments to facilitate subsequent discrimination between data fits to homogeneous and inhomogeneous lung models (inhomogeneity being taken as alveolar deadspace in this application).

In section 8.5 the proposed approach to the structure discrimination experiment design problem was outlined and an intuitively reasonable criterion function for this purpose developed, based on hypothesis testing considerations. It was also shown that in order to use the proposed approach, the theory makes it necessary that the simpler of the two competing models can be expressed as a special case of the more general model so that the zero null hypothesis test can be suitably defined. Thus at this stage it is pertinent to investigate if our problem can be formulated in such a manner. In fact it can be, as we shall show, provided the inhomogeneous gas transport model is suitably reparameterised.

Recall from section 8.3 the parameter vector for the five parameter inhomogeneous model was :-

$$\theta = \left[\dot{Q} , V_A , V_{T_C} , V_{A_D} , k \right]^T \qquad 8.70$$

where these quantities are defined as earlier.

By employing the linear transformation

$$\beta = A\,\theta + b \qquad 8.71$$

with $$b = \left[0 \quad 0 \quad 0 \quad 0 \quad 1 \right]^T \qquad 8.72$$

and

$$A = \begin{bmatrix} 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & -1 \\ 1 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 \end{bmatrix} \qquad 8.73$$

This gives the reparameterised model vector β as

$$\beta = \left[V_{A_D} , 1 - k , \dot{Q} , V_A , V_T \right]^T \qquad 8.74$$

Reparamterising the model in this way then allows us to use the hypothesis testing approach discussed in section 8.5. Notice that with the model in this form testing the null hypothesis Ho

$$\text{Ho}: \beta_1 = \begin{bmatrix} V_{A_D} \\ 1 - k \end{bmatrix} = 0 \qquad 8.75$$

is equivalent to testing the hypothesis that the homogeneous inert gas model is preferred to the inhomogeneous one since under the restriction given by equation 8.75 the inhomogeneous model and homogeneous model become essentially the same.

The four parameter inhomogeneous model, with which we are principally concerned in this section can be similarly reparameterised for

use with the theory developed in section 8.5, i.e. by arranging β into the form

$$\beta = \left[V_{A_D} , \dot{Q} , V_A \; V_{Tc} \right]^T \qquad 8.76$$

then testing the hypothesis

$$Ho : \beta_1 = \left[V_{A_D} \right] = 0 \qquad 8.77$$

allows us to ascertain if the homogeneous model is preferred to the inhomogeneous model.

If it is assumed the measurement noise is white then the D_s optimal criterion as given in equation 8.77 reduced in this particular application to the following :-

$$J_s = \left[X_{\beta_1}{}^T X_{\beta_2} - X_{\beta_1}{}^T X_{\beta_2} \left(X_{\beta_2}{}^T X_{\beta_2} \right)^{-1} X^T{}_{\beta_1} X_{\beta 2} \right] \qquad 8.78$$

with $\beta_1 = V_{A_D}$ 8.79

and $\beta_2 = \begin{bmatrix} \dot{Q} \\ V_A \\ V_{Tc} \end{bmatrix}$ 8.80

Notice that this criterion could equally well be interpreted as a truncated D optimal criterion (see Chapter 7) with V_{A_D} the only parameter of interest in the model.

In fact, it can be shown (18) that in this case, due to the fact β_1 is scalar, all the different discrimination criteria based on hypothesis testing mentioned in section 8.5 (i.e. T optimal, minimax, etc.) are essentially equivalent and reduce to such a truncated D optimal criterion.

In order to investigate the best form of experiment to use for structure discrimination, the simulation programme written for the inhomogeneous model was extended to allow the D_s criterion and related quantities to be calculated for various sets of parameters and design strategies

of interest. The present experimental design study differs from that in Chapter 7 since, in using an inert gas model, it has been implicitly assumed that the solubility coefficient of the inert gas λ is a design parameter at our disposal and can be suitably chosen, in addition to the frequency of the input square wave τ, to enhance structure discrimination. That is in this application the design space is two dimensional. It is apparent from this that the design of the discrimination experiment could easily be treated as a function minimisation problem and a solution found using the generalised function minimisation package described in Appendix B. However, there are difficulties in using the minimisation package directly in this context, due to the integer nature of the square wave period τ (which must be a whole number of breaths). This approach has therefore not been pursued. In practice, only the variation of discrimination criterion in one dimension (i.e. with one design parameter with the other fixed and vice versa) has been investigated, which is felt to be sufficient in this situation. In view of the uncertainty as to exact model parameter values a priori, or even which model is the 'true' model, we are only really concerned with inferring the gross nature of a good discrimination experiment rather than an 'optimal' one.

The set of parameter values and constant experimental conditions chosen for the design study were as follows :-

model parameters : $\dot{Q}$ = 5 L/M ; V_A = + 2L; V_{T_C} = 7.5 L; V_{A_D} = 1 L.

const. experimental conditions : $\dot{V}$ = 8 L/M ; V_D = 0.2 L ; breathing frequency = 15 breaths/M; no. of breaths in expt. = 130 ; max. inspired gas input concentration = 7%.

This thus corresponds to a 13 minute experiment.

The variation of the D_s optimal criterion with square wave switching period

is tabulated in Table 8.1 for fixed solubility coefficient (λ = 2.0). This is illustrated graphically in Figure 8.9. The variation with τ of the D optimal criterion and the D_t optimal criteria for Q ; V_A and V_{T_C} are also tabulated in Table 8.1 for comparison.

These results show an extremum for the D_s criterion does exist at a switching period τ of around 16 breaths which is similar to the 'best' switching period for the D optimal criterion (which attempts to design experiments which give a best fit to the model as a whole).

Now consider the variation of the discriminating criterion with switching period τ for a lower solubility inert gas (λ = 0.01). This is tabulated, along with the other criteria mentioned above in Table 8.2 and plotted in Figure 8.10. It is immediately apparent from these latter results that there is a large increase in the discriminating criterion at all τ using the lower, as opposed to the higher, solubility gas. From Figure 8.10 we also see that the 'optimal' switching period at this solubility is increased to 26 breaths. This change in the 'best' τ at different λ shows that there is in fact some interaction between the experimental design parameters although the magnitude of the change shows this coupling is not too great.

In Table 8.3 the variation of the D_s criterion with λ for τ fixed (at τ = 40 breaths) is considered. This is also plotted in Figure 8.11. These results tend to confirm the findings above that model discrimination is markedly better using low solubility test gases. In fact, this correlates with the published findings of Farhi and Yokohama (103) for steady state inert gas elimination. These authors showed low solubility gases were better for detecting pulmonary units with high $\dot{V}/\dot{Q}$ ratio (i.e. 'alveolar dead space like' regions with which we are specifically concerned in this application as regards discrimination).

Table 8.1

Variation of D_s Optimal Criterion, D Optimal Criterion and D_t Optimal Criteria (Assuming $\dot{Q}$, V_A and V_{T_C} Respectively Are Primary Parameters of (Interest) with Inspired Gas Concentration Switching Period

($\lambda = 2.0$)

Switching Period (τ) (Breaths)	D_t Opt. Critn. ($\dot{Q}$)	D_t Opt. Critn. (V_A)	D_t Opt. Critn. (V_{T_C})	D_S Opt. Critn.	D Opt. Critn.
4	41.5	52.5	17.8	138.7	2.1×10^8
6	60.7	60.9	20.9	186.6	4.3×10^8
8	88.2	70.0	25.7	239.8	8.4×10^8
10	116.7	64.9	26.5	283.4	1.2×10^9
16	180.6	55.6	27.3	332.2	2.1×10^9
18	187.9	52.3	26.5	326.2	2.2×10^9
20	193.6	46.4	24.6	208.6	2.1×10^9
26	194.0	35.6	23.5	309.6	1.9×10^9
30	189.3	34.5	21.8	271.8	1.8×10^9
40	174.1	29.9	21.1	224.0	1.5×10^9
50	127.0	21.8	20.5	193.1	1.4×10^9

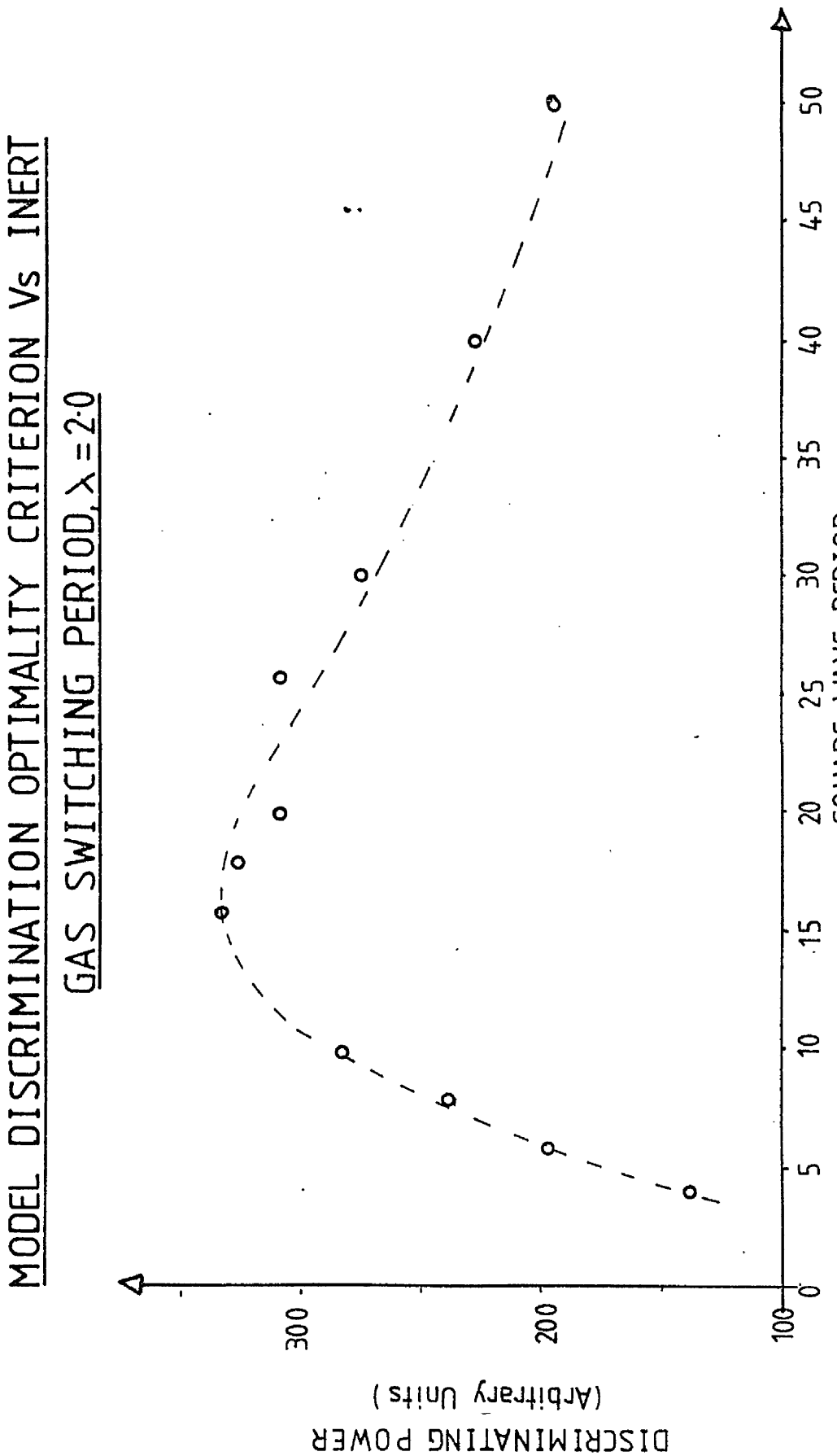

MODEL DISCRIMINATION OPTIMALITY CRITERION Vs INERT
GAS SWITCHING PERIOD, λ=2·0
DISCRIMINATING POWER
(Arbitrary Units)
100
200
300
0
5
10
15
20
25
30
35
40
45
50
SQUARE WAVE PERIOD
(BREATHS)

FIGURE 8·9

Table 8.2

Variation of D_s Optimal Criterion, D Optimal Criterion and D_t Optimal Criteria (Assuming $\dot{Q}$, V_A and V_{T_C} Respectively are Primary Parameters of Interest) with Inspired Gas Switching Period

(λ = 0.01)

Switching Period (τ) (Breaths)	D_t Opt. Critn. ($\dot{Q}$)	D_t Opt. Critn. (V_A)	D_t Opt. Critn. (V_{T_C})	D_s Opt. Criterion	D Opt. Criterion
4	0.019	237.0	0.013	324.3	1.87×10^2
6	0.024	318.4	0.007	478.7	1.95×10^2
8	0.026	388.6	0.011	722.3	4.53×10^2
10	0.033	496.3	0.011	901.4	7.73×10^2
16	0.051	638.6	0.012	1517.9	2.23×10^3
18	0.061	678.7	0.013	1676.6	3.40×10^3
20	0.065	807.1	0.017	1574.6	5.36×10^3
26	0.100	559.3	0.014	2011.5	8.72×10^3
30	0.109	558.2	0.013	1859.9	1.11×10^4
40	0.126	485.4	0.014	1538.5	1.34×10^4
50	0.160	316.5	0.14	1202.5	1.29×10^4

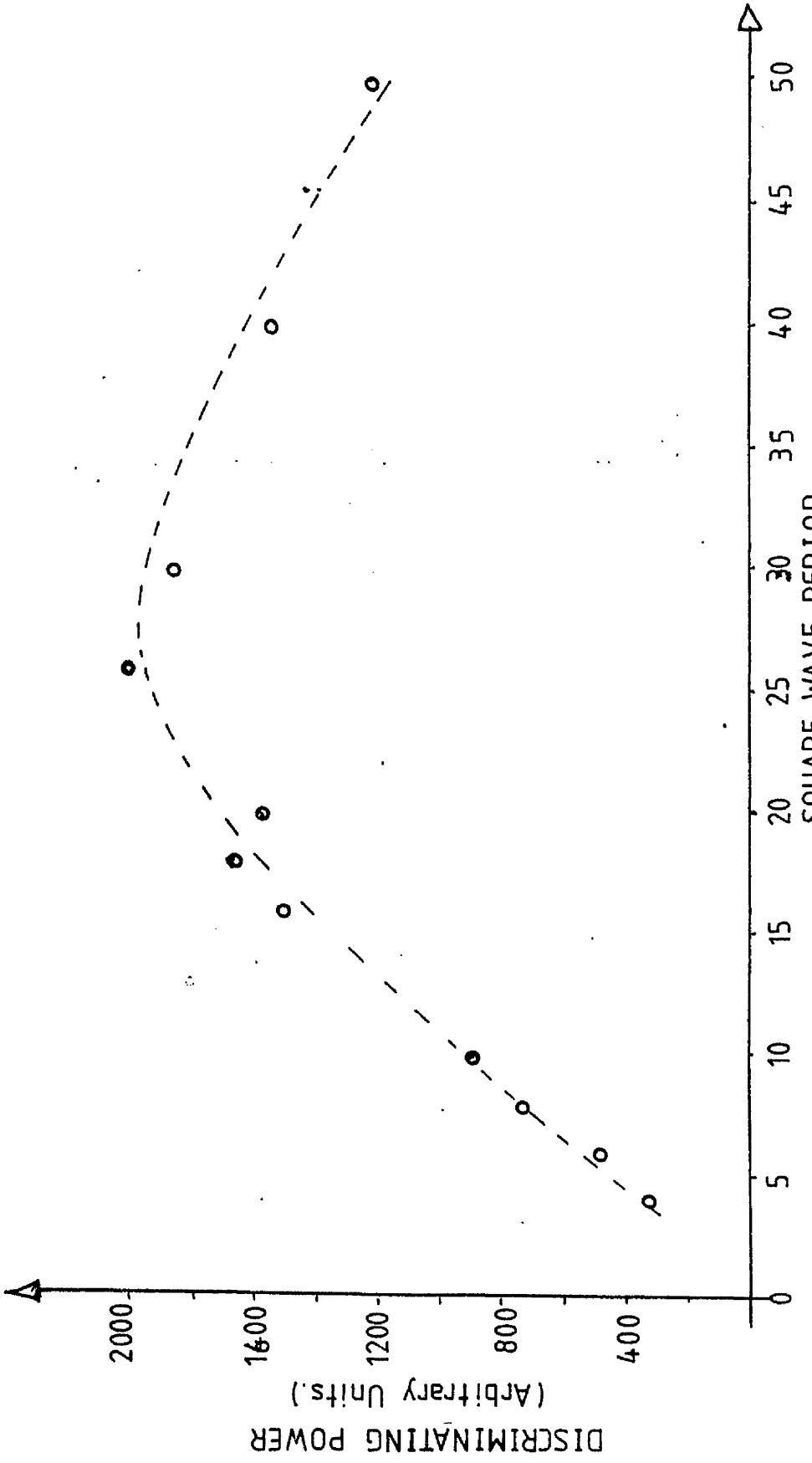

MODEL DISCRIMINATION OPTIMALITY CRITERION Vs INERT
GAS SWITCHING PERIOD, λ = 0·01
DISCRIMINATING POWER
(Arbitrary Units.)
2000
1600
1200
800
400
0
5
10
15
20
25
30
35
40
45
50
SQUARE WAVE PERIOD
(BREATHS)

FIGURE 8·10

Table 8.3

Variation of D_s Optimal Criterion, D Optimal Criterion and D_t Optimal Criteria (Assuming $\dot{Q}$, VA, V_{T_C} Respectively are Primary Parameters of Interest) with Inert Gas Solubility Coefficient

(τ = 40 breaths)

Solubility (λ)	D_t Opt. Critn. ($\dot{Q}$)	D_t Opt. Critn. (VA)	D_t Opt. Critn. (V_{T_C})	D_s Opt. Criterion	D Opt. Criterion
0.01	0.126	485.0	0.014	1537.6	1.34×10^4
0.1	10.15	406.7	1.0	1350.6	6.60×10^7
0.47	101.6	223.2	10.3	809.7	3.18×10^9
2.0	174.1	29.9	21.1	224.0	1.5×10^9
3.0	42.8	11.1	20.2	99.0	4.5×10^8
4.0	13.6	5.5	21.0	34.9	1.8×10^8
5.0	6.8	3.8	24.9	16.1	9.6×10^7
7.0	4.8	3.7	45.5	9.6	6.1×10^7
10.0	6.1	6.0	84.0	10.9	5.7×10^7

MODEL DISCRIMINATION OPTIMALITY CRITERION Vs INERT GAS SOLUBILITY COEFFICIENT, τ=40 BREATHS.

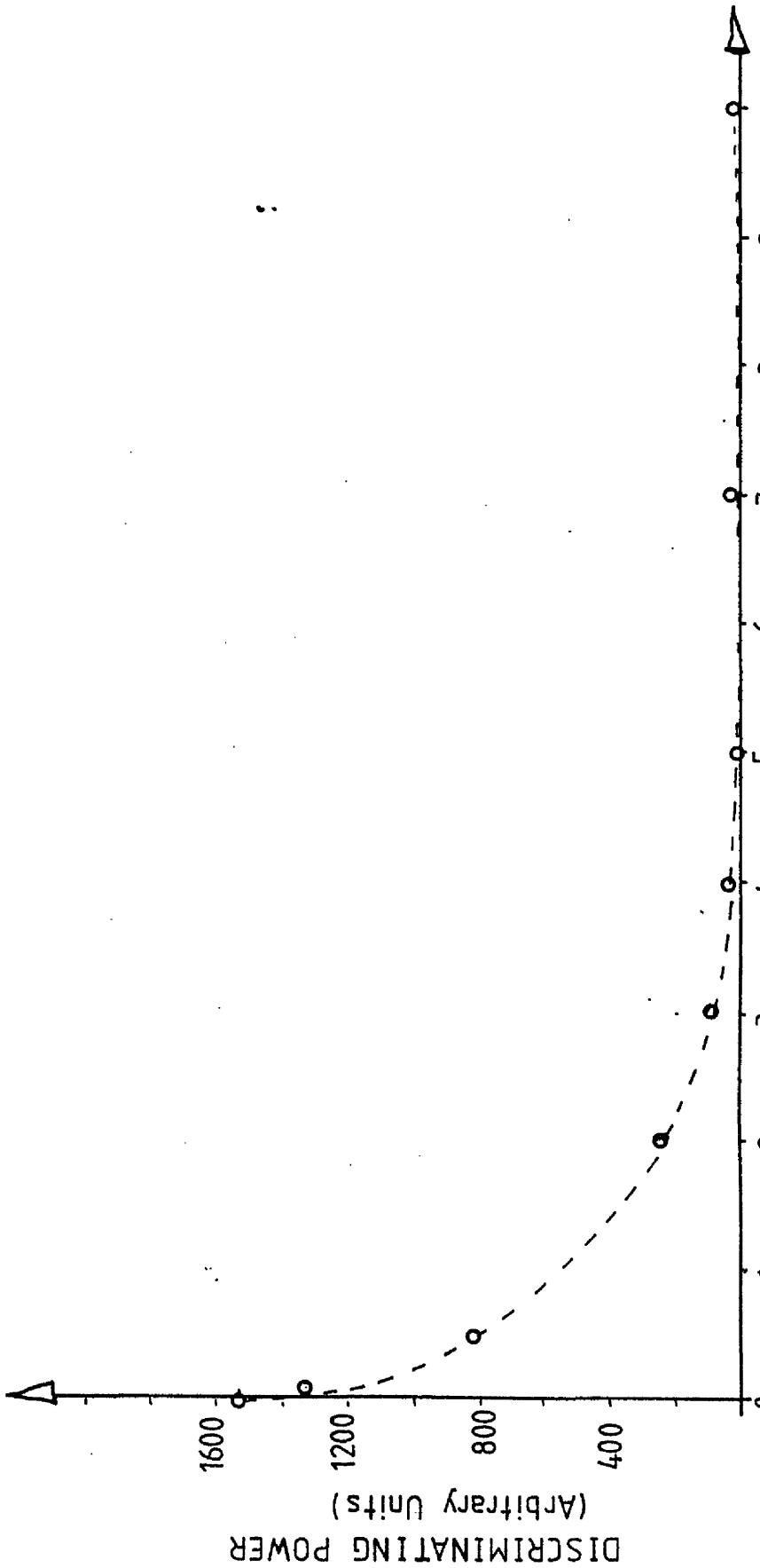


FIGURE 8·11

For good resolution among the two competing models, one would intuitively expect the experimental conditions to be such that the difference between the 'true' model and the model against which we are trying to discriminate should be as large as possible. It was therefore considered important to investigate whether the form of experiments dictated by the D_s optimal criterion possessed this kind of reassuring characteristic. To explore this possibility the output of the inhomogeneous model with parameters, experimental conditions, etc. as given above, (i.e. in particular it assumes the alveolar regions are split in a 2 L ideal compartment and 1L alveolar deadspace compartment), was compared with a homogeneous model with a 3L alveolar volume and otherwise similar parameters as to the homogeneous model.

The variation of the mean sum of squares of the resultant differences between the two models (i.e. $\frac{\sum_{i=1}^{NBR} (y_{M1} - y_{M2})^2}{NBR}$) for varying λ (at fixed τ = 40 breaths) is tabulated in Table 8.4. By comparing these results with those in Table 8.3 it is seen a large value of the D_s optimal criterion is in fact synonimous with a large output difference between the two competing models. This is interesting since Beck and Arnold (22) starting with a specific initial objective of designing experiments which cause the outputs of the two models in question to be maximally different, arrive at a model discrimination criterion similar to the D_s optimal criterion derived in Section 8.5 of this chapter on hypothesis testing considerations.

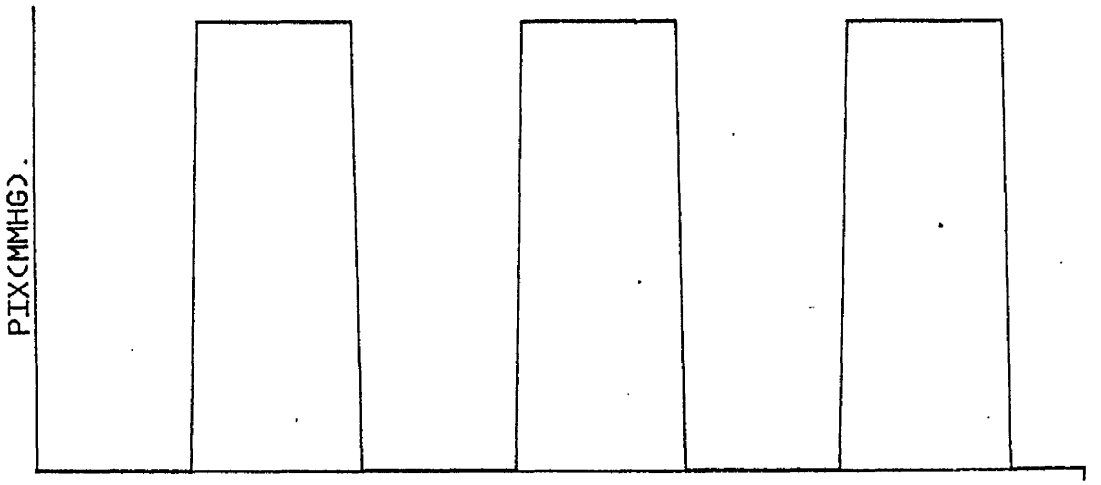
In Figure 8.12 the output of the homogeneous and inhomogeneous models for the same inputs are shown superimposed, both for λ = 0.01 and λ = 16.0. From this diagram the increase in difference in the model

Table 8.4

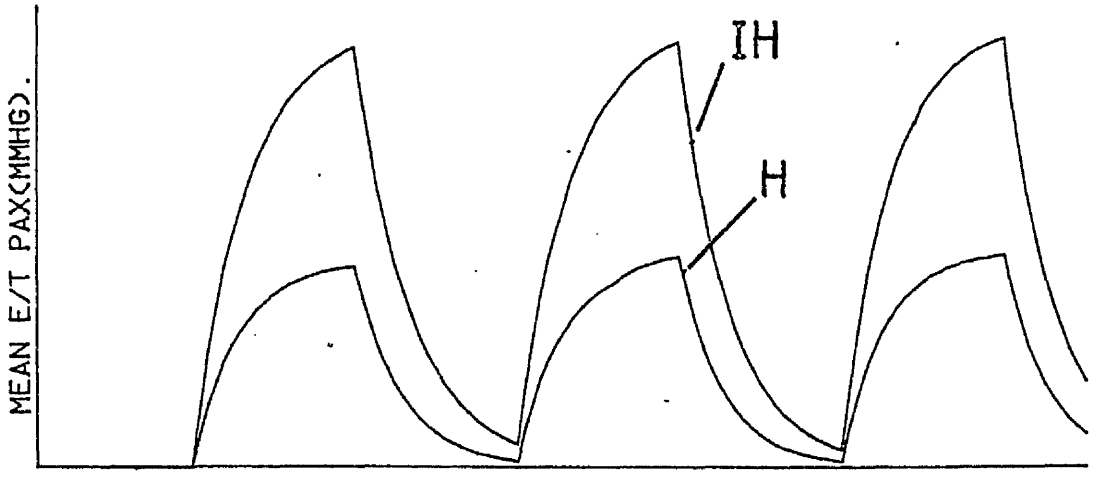
Variation of Mean Sum of Square Difference Between Outputs of Homogeneous and Inhomogeneous Model with Inert Gas Solubility Coefficient (τ = 40 Breaths).

Solubility (λ)	$\sum \frac{(Y_{M_1} - Y_{M_2})^2}{NBR}$ (mmHg)
0.01	235.8
0.1	227.2
0.47	195.8
2.0	114.8
3.0	85.2
4.0	65.3
5.0	50.5
7.0	32.1
10.0	17.6

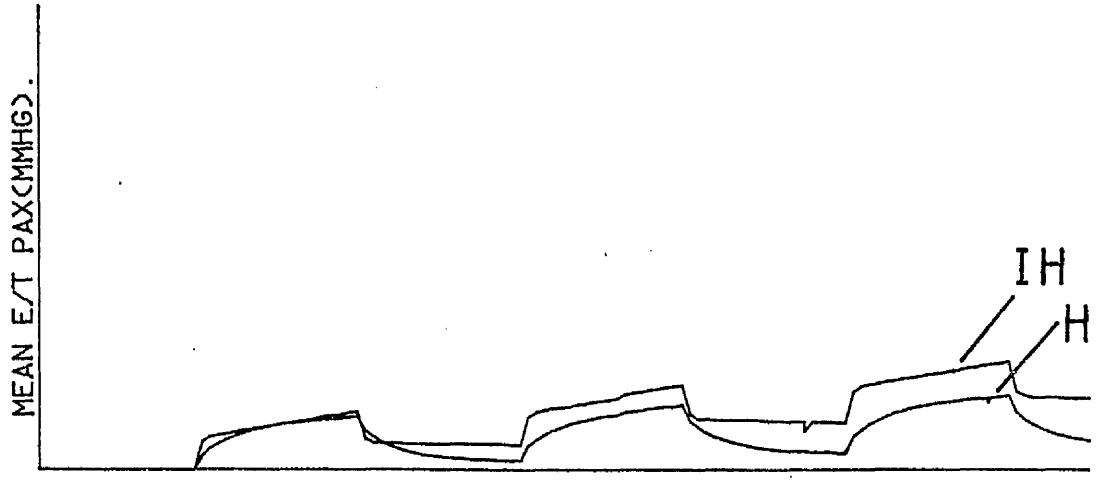
HOMOGENEOUS/INHOMOGENEOUS MODEL RESPONSES.



INSPIRED SQ WAVE INPUT.



SOLUBILITY COEFFICIENT =0.01.



SOLUBILITY COEFFICIENT =16.0.

FIGURE 8·12

outputs using a low rather than high solubility gas can be clearly appreciated. Notice that at $\lambda = 0.01$ in the above the r.m.s. difference between the models is of the order of 15 mm Hg. This is a large difference when one considers that a good respiratory mass spectrometer is typically accurate to around $\pm$ 0.1 mm Hg.

To summarise then, the above studies, although merely prefatory, have at the very least served to illustrate that the application of the techniques outlined in this chapter to the early detection of ventilatory lung inhomogeneity is a fruitful avenue for further research - both theoretical and practical. The most pressing need in this respect is to carry out some real live identification experiments based on the results of this preliminary simulation study. These could easily be carried out using the models and software already developed for use in the work described in this thesis and utilising the experiment rig and on-line data acquisition system at the Centre for Respiratory Investigation.

CHAPTER 9

CONCLUSIONS

This project arose as part of a continuing programme of research being carried out by staff in the Control Group in the Department of Electronics and Electrical Engineering at Glasgow University in conjunction with medical and scientific personnel at the Centre for Respiratory Investigation, Glasgow Royal Infirmary.

The unifying theme of this collaboration was the belief that current methods of analysing respiratory function could be improved by more enlightened mathematical treatment of measured pulmonary data. Recent advances in signal processing techniques and the availability of increasingly low cost computing power have served to enhance this perspective.

One area of this research involved development of a new technique for indirect measurement of cardio-pulmonary parameters using only measurements of gas concentrations and ventilatory flow rate at the mouth. The clinicians had focussed on the measurement of cardiac output as being of specific interest since traditional techniques of measuring this are invasive and therefore involve some discomforture for the patients.

Prior to the involvement of the author in this project, a homogeneous CO_2 gas transport model had been developed for use in this technique and some preliminary validation experiments had been carried out with limited success. That is, although the resultant measurements showed reasonable mean agreement with results obtained using a more direct method (dye-dilution) the reproducibility was inferior to that anticipated on the basis of such a mathematical technique.

Thus, this Ph.D. project was commissioned to investigate in a more rigourous way than done previously, the parameter estimation aspects of

the technique with the primary aim of uncovering mechanisms to increase the reproducibility of the non-invasive measurement method.

In response to the question "Did the project fulfil the aims desired of it at its inception ? " , the author is confident he can answer an unequivocal "yes". The justification for this is the improved reproducibility of the model-based cardiac output measurement technique resulting from using the new form of test procedure derived from this project. Average reproducibility of the earlier validation studies was 12.2% for the model-based technique and 6.8% for the dye dilution technique. In contrast, the results obtained from the later reproducibility studies using the new test are summarised in Table 9.1.

This table shows clearly the improvements obtained using the new test procedure with the average reproducibility being 4.6% (if the 'rogue' results for subject CN. are ignored). It transpires such a figure can in fact be compared favourably with the results obtained at rest by any other technique which has hitherto appeared in the literature (non-invasive or invasive). This is illustrated in Table 9.2 where the results obtained by the technique are compared with the relevant results extracted from Table 3.1 of Chapter 3. These promising results positively encourage the hope that the model-based cardiac output measurement method might eventually aspire to the status of being a routine clinical tool. Before this happens, however, further definitive validation studies are required to consolidate the good reproducibility results. This is obviously the logical direction for the work to progress in. Such a study is shortly to be undertaken at C.R.I.

Table 9.1

Reproducibility Results Obtained From Series of 10 min. Cardiac Output Estimations Expts.

Subject	Reproducibility - 5% CO_2 (CV %)		Reproducibility - 7% CO_2 (CV %)
RB (M)	REPØ2 5.1 %		REPØ1 2.2 %
RB (M)	REPØ7 4.8 %		REP 12 2.3 %
R M^C C (F)	REPØ9 10.2 %		REP 11 4.6 %
C M^C S (M)	REP 19 4.2 %		REP 18 5.4 %
SN (F)	REP 2Ø 3.2 %		REP 14 4.0 %
MEAN	5.5 %	4.6 %	3.7 %
CN (F)	REPØ8 12.3 %		REP15 16.4 %
OVERALL MEAN	6.6 %	6.2 %	5.8 %

Table 9.2

Reproducibility Results Obtained From Various Cardiac Output Measurement Techniques at Rest

Investigation	Method	Coefficient of Variation
Franciosa et al (122)	Dye Dilution	6.5 %
Franciosa et al (122)	Collier CO_2 re-breathing	6.0 %
Ferguson et al (109)	Defares CO_2 re-breathing	13.3 %
Glasgow University/ C.R.I.	Parameter Estimation based on CO_2 Gas Exchange Model.	4.6 %

Further areas in which research outlined in this thesis could be extended are discussed below.

One very obvious area is the application of identification methods to inhomogeneous lung models as discussed in Chapter 8. Here much experimental work remains to be done to ascertain if the structural model discrimination technique suggested is sufficiently sensitive to form the basis of a routine test to differentiate between normal and diseased lungs at a clinically useful stage. Further theoretical investigation could take the form of looking at the suitability of other forms of discrimination criteria from that eventually used in Chapter 8. For example, the information-theoretic approach (38). Whilst still discussing the prospects in this area, it is also worth noting that recent advances in blood-gas probes (33, 94) are such that in vivo blood gas analysis may soon be within the state of the art. In fact, some tentative studies in this direction have already been reported in the physiological literature (204). The new mass spectrometer used at the C.R.I. for the work described in this thesis (see Chapter 3) is capable of being used with such probes should reliable versions become commercially available.

The possibility of being able to continuously measure mixed venous and arterial gas partial pressures should make the investigation of lung inhomogeneity by system identification techniques an even more feasible proposition. That is, the availability of such measurements should permit perfusion orientated inhomogeneities to be quantified which would be hitherto unidentifiable by measurements at the mouth only (see Chapter 8). Another possibility for further work is developing a recursive identification scheme for use with the homogeneous CO_2 model to allow cardiac output to be tracked in a situation where it is time-varying. This would form a logical

continuation of the off-line work described in this thesis and might find applicability e.g. in physiological studies of cardiac output dynamics under exercise, etc.

Such work would probably be able to take advantage of recent big advances in recursive identification algorithms (162, 264, 192) and of improved tools for their analysis (188, 189). The impetus for this advancement is the interest in stochastic adaptive controllers (299, 12) in an industrial process context. The numerical methods community have tended to view many of these recursive identification techniques with some disdain (e.g. the Kalman filter) due to rumours of their poor numerical properties (32). Thus, bearing in mind numerical experiences with the off-line function minimisation methods in this thesis it would be advisable to devote some attention to these aspects of the equivalent recursive methods. Some work has been reported on the development of numerically stable algorithms based on the advantageous properties of triangular systems (31) which is worthy of attention in this respect. The author envisages an advantageous way of augmenting the recursive estimation technique might be by cascading it with a one step ahead test signal design 'control law' as depicted in Figure 9.1.

This would increase the 'learning rate' of the scheme over that obtained utilising a test signal fixed in advance. Such sequential optimal experimental design techniques were briefly introduced in Chapter 7 (6, 174). Two disadvantages of these methods for our envisaged application are the following. The first is that the criteria are based on a model linear in the parameters and the second is that they are based on the assumption of all the parameters being of interest for identification (i.e. D optimal criterion). However, some preliminary studies by the author

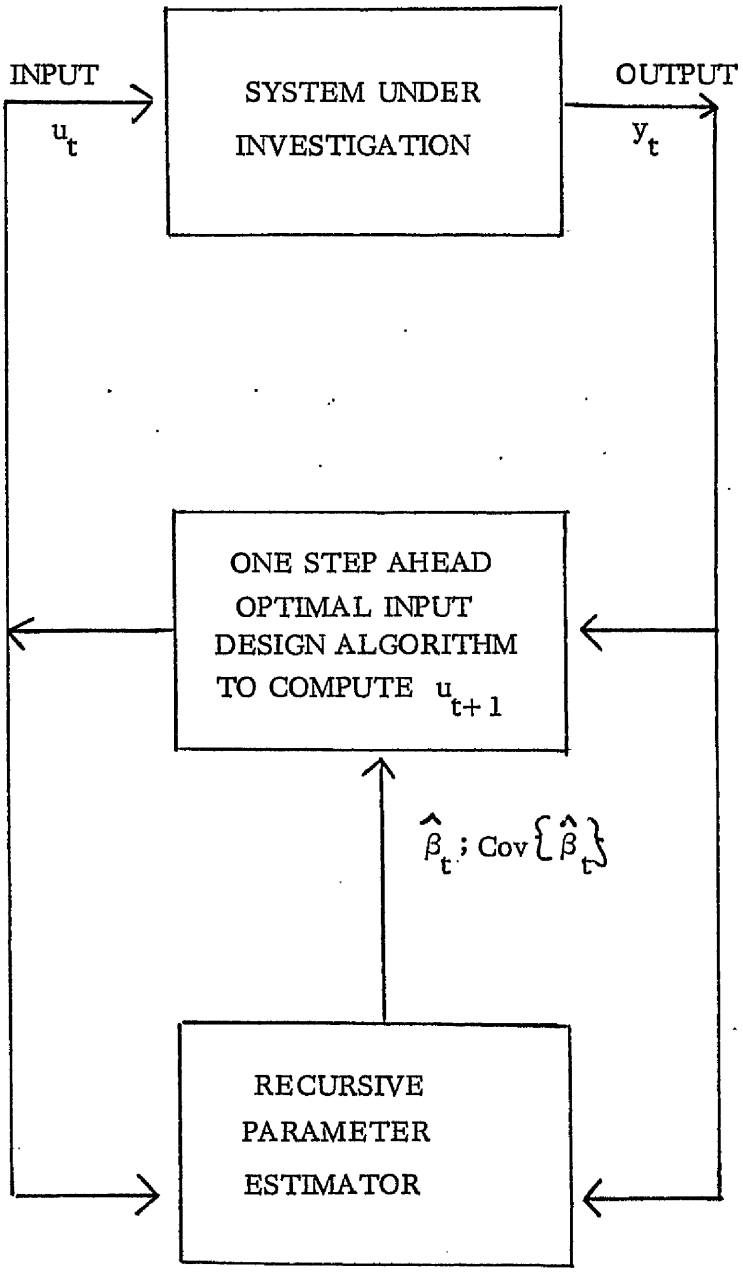


FIGURE 9.1

PROPOSED RECURSIVE IDENTIFICATION SCHEME

(not included in this thesis) have shown these can be successfully adapted for models non-linear in the parameters and in conditions under which only a subset of the parameters are of specific interest, such as pertain to this envisaged application.

Whilst discussing the potential of recursive cardiac output estimation, it is appropriate to mention the work of Brovko et al (47) which has only recently come to the attention of the author on this very topic.

The approach has been inspired by the work of Zwart et al (309) and the model used is concomitant with that developed by these authors. In the technique, the extended Kalman filter (3) as improved by Ljung (190) is used as the estimator. The form of test signal is chosen a priori. Preliminary results reported (47) seem to be extremely encouraging although the method requires more experimental validation before it can be assessed accurately.

Finally, yet another area into which the work could usefully progress is the study of the respiratory control system via identification techniques. Work has already been undertaken in this area elsewhere (e.g. that of Swanson (272)). However, in much of this, despite complex mathematics, e.g. in the description of the respiratory 'plant', the controller itself has in essence been represented by simple empirical steady state equations with an output taken as minute ventilation. However, contemporary physiologists are beginning to be of the opinion that assuming minute ventilation as the output index of respiratory controller behaviour is too gross for the study of a system which is after all cyclic (74) and are advocating attention should be focussed on the within breath ventilatory controller manifestations. That is, those of the tidal volume/breath cycle timing sequence generator.

In an associated project in collaboration with the Department of Electronics and Electrical Engineering and C.R.I. Greer (140) has carried out simulation work on models incorporating such mechanisms, although not via statistical identification techniques. Thus it is felt a study of the respiratory controller by applying estimation techniques to the models developed by Greer would be an area ripe for further research.

In fact, in the data collected for use in this project (i.e. see Chapter 7) the inherent ventilatory response to the hypercapnic stimulus inherent in these files could conceivably have enough information content to permit preliminary identification studies to be carried out without recourse to further experimentation. It is perhaps appropriate to finish this chapter on the following note. It was mentioned in Chapter 1 of this thesis that there is a great reluctance at present for clinicians to take the use of control engineering techniques seriously in the context of practical biomedicine. It is the author's hope that the work presented in this thesis will be seen as lending further weight to the increasing body of evidence that quantitative control methods have in fact a significant role to play in the biomedical area.

REFERENCES

1. ADBY, P.R., M.A.H. Dempster, (1974).
Introduction to optimisation methods.
Chapman and Hall, London, England.

2. AKAIKE, H. (1974).
A new look at statistical model identification.
I.E.E.E. Transactions Automatic Control, 19 : 716-723.

3. ANDERSON, B.D.O., J.B. Moore, (1979).
Optimal Filtering, Chapter 8.
Prentice-Hall, New Jersey, U.S.A.

4. ANDREWS, D.F. (1971).
Sequentially designed experiments for screening out bad models with F-tests.
Biometrika. 58 : 427-432.

5. AOKI, M., R.M. Staley, (1969).
On input signal synthesis in parameter identification.
Automatica. 6 : 431-440.

6. ARIMOTO, S., H. Kimura, (1971).
Optimum input test signals for system identification - an information - theoretic approach.
International Journal of Systems Science. 1 : 279 - 290.

7. ASHTON, C.H., G.J.R. McHardy, (1963).
A rebreathing method for determining mixed venous PCO_2 during exercise.
Journal of Applied Physiology. 18 : 668 - 671.

8. ASMUSSEN, E., M. Neilsen, (1953).
The cardiac output in rest and work determined simultaneously by the acetylene and dye dilution methods.
Acta Physiologica Scandanavia. 27 : 217 - 230.

9. ASTROM, K.J., (1970).
Introduction to stochastic control theory.
Academic Press, New York, U.S.A.

10. ASTROM, K.J., (1967).
Computer control of a paper machine - an application of linear stochastic control theory.
I.B.M. Journal of Research and Development, 11 : 389 - 405.

11. ASTROM, K.J., T. Bohlin, (1966).
Numerical identification of linear dynamic systems from normal operating records. In Theory of self-adaptive control systems, Hammond, P.H. (Editor), Plenum Press, New York, U.S.A.

12. ASTROM, K.J., U. Borisson, L. Ljung, B. Wittenmark, (1977).
Theory and applications of self-tuning regulators.
Automatica, 13 : 457 - 476.

13. ASTROM, K.J., P. Eykhoff, (1971).
System identification - a survey.
Automatica, 7 : 123 - 162.

14. ASTROM, K.J., C.G. Kallstrom, (1976).
Identification of ship steering dynamics.
Automatica, 12 : 9-22.

15. ASTROM, K.J., B. Wittenmark, (1973).
On self-tuning regulators.
Automatica, 9 : 185-199.

16. ATKINSON, A.C., (1972).
Planning experiments to detect inadequate regression models.
Biometrika, 59 : 275-293.

17. ATKINSON, A.C., D.R. Cox, (1974).
Planning experiments for discriminating between models.
Journal of Royal Statistical Society, B.36 : 321-348.

18. ATKINSON, A.C., V.V. Federov, (1975).
The design of experiments for discriminating between two rival models.
Biometrika, 62 : 57-70.

19. AYOTTE, B., J. Seymour, M.B. McIlroy, (1970).
A new method for measurement of cardiac output with nitrous oxide.
Journal of Applied Physiology. 28 : 863-866.

20. BALL, W.C., P.B. Stewart, G.S. Newsham, D.V. Bates, (1962).
Regional pulmonary function studied with xenon^{133}.
Journal of Clinical Investigation, 41 : 519-531.

21. BAR-SHALOM, Y., E. Tse, (1974).
Dual effect, certainty equivalence and separation in stochastic control.
I.E.E.E. Transactions Automatic Control. 19 : 494-450.

22. BECK, J.V., K.J. Arnold, (1977).
Parameter estimation in engineering and science.
John Wiley, New York.

23. BECKLAKE, M.R., C.J. Varvis, L.D. Pengally, S. Kenning,
M. McGregor, D.V. Bates, (1962).
Measurement of pulmonary blood flow during exercise using
nitrous oxide.
Journal of Applied Physiology. 17 : 579-586.

24. BEKEY, G.A. (1970).
System identification - an introduction and survey.
Simulation. 15 : 151-166.

25. BEKEY, G.A., (1973).
Parameter estimation in biological systems : a survey.
In preprints 3rd IFAC Symposium on Identification and System
Parameter Estimation. Held, Delft, Holland.

26. BEKEY, G.A., J.E.W. Beneken, (1978).
Identification of biological systems : a survey.
Automatica. 14 : 41-47.

27. BEKEY, G.A., S.M. Yamashiro, (1976).
Parameter estimation in mathematical models of biological
systems. In Advances in biomedical engineering,
Vol. 6, Academic Press, New York, U.S.A.

28. BELLMAN, R., K.J. Astrom, (1970).
On structural identifiability.
Mathematical Biosciences. 7 : 329-339.

29. BELLVILLE, J.W., B.J. Whipp, R.D. Kaufman, G.D. Swanson, K.A. Agleh, D.M. Wiberg, (1979).
Central and peripheral cheomoreflex loop gain in normal and carotid body-resected subjects.
Journal of Applied Physiology, Respiratory, Environmental and Exercise Physiology. 46 : 843-853.

30. BENDAT, J.C., A.C. Piersol,(1966).
Measurement and analysis of random data.
John Wiley, New York, U.S.A.

31. BIERMAN, G.J., (1976).
Measurement updating using the U-D factorisation.
Automatica, 12 : 375-382.

32. BIERMAN, G.J., C.L. Thornton, (1977).
Numerical comparisons on Kalman filter algorithms : orbit determination case study.
Automatica, 13 : 23-25.

33. BLACKBURN, J.P., (1978).
What is new in blood gas analysis ?
British Journal of Anaesthesia. 50 : 51-62.

34. BOCK, A.V., H. Field, G.S. Adair, (1924).
The oxygen and carbon dioxide dissociation curves of human blood.
Journal Biological Chemistry, 59 : 353-377.

35. BOHLIN, T. (1978).
Maximum-power validation of models without higher order fitting.
Automatica. 14 : 137-146.

36. BOOTH, A.D. (1957),
Numerical Methods.
Butterworths, London.

37. BOWEN, H.C., R.J. Fenton, M.A.M. Rogers, R.D. Hurrion, R.J.R. Secker, (1979).
Interactive computing as an aid to decision - makers.
In O.R.' 78, Halley, K.B. (Editor), North Holland.

38. BOX, G.E.P., W.J. Hill, (1967).
Discrimination among mechanistic models.
Technometrics, 9 : 57-71.

39. BOX, G.E.P., G.M. Jenkins, (1970).
Time series analysis : forecasting and control.
Holden-Day, San Francisco.

40. BOX, G.E.P., H.L. Lucas, (1959).
Design of experiments in non-linear situations.
Biometrika. 46 : 77-90.

41. BOX, M.J., D. Davies, W.H. Swann, (1969).
Non-linear optimisation techniques.
I.C.I . Monograph No. 5, Oliver and Boyd, Edinburgh.

42. BRIGGS, P.A.N., D.W. Clarke, P.H. Hammond, (1968),
Introduction to statistical identification methods in control systems.
Control, March Issue.

43. BRIGGS, P.A.N., K.R. Godfrey, P.H. Hammond. (1967).
Estimation of process dynamics characteristics by correlation methods using pseudo-random test signals. In Preprints 1st IFAC Symposium on Identification and Process Parameter Estimation.
Held at Prague, Czechoslavakia.

44. BRISCOE, W.A., E.M. Cree,J. Filler, J.E.H. Houssay, A. Cournand, (1960).
Lung volume, alveolar ventilation and perfusion interrelationships in chronic pulmonary emphysema.
Journal of Applied Physiology, 15 : 785-795.

45. BRISCOE, W.A., A. Cournand, (1959).
Uneven ventilation of normal and diseased lungs studied by an open-circuit method.
Journal of Applied Physiology, 14 : 284-290.

46. BRISCOE, W.A., E.S. Nash, (1965).
The slow space in chronic obstructive pulmonary disease.
Annals New York Academy of Science, 121 : 706-722.

47. BROVKO, O., D.M. Wiberg, L. Arena, J.W. Bellville, (1979).
The extended Kalman filter as a pulmonary blood flow estimator.
In Preprints 5th IFAC Symposium on Identification and system parameter estimation.
Held at Darmstadt, Federal Republic of Germany.

48. BROWN, J.C., E. Rose, (1976).
Hybrid simulation of thermal processes during sintering.
In Simulation of Systems, Dekker, L. (Editor), North Holland.

49. BROWN, R.F., K.R. Godfrey, (1978).
Problems of determinancy in compartmental modelling with application to bilirubin kinetics.
Mathematical Biosciences. 40 : 205-224.

50. BROYDEN, C.G. (1965).
A class of methods for solving non-linear equations.
Mathematics of Computation, 19 : 577-584.

51. BROYDEN, C.G., (1967).
Quasi-Newton methods and their application to function minimisation.
Mathematics of Computation. 21 : 368-381.

52. BROYDEN, C.G. (1970).
The convergence of a class of double rank minimisation algorithms part I : general considerations.
Journal of the Institute of Mathematics and its Applications. 6 : 66-90.

53. BROYDEN, C.G. (1970).
The convergence of a class of double rank minimisation algorithms part II : the new algorithm.
Journal of the Institute of Mathematics and its Applications. 6 : 222-231.

54. BURWELL, C.S., G.C. Robinson, (1924).
A method for the determination of the amount of oxygen and carbon dioxide in the mixed venous blood of man.
Journal of Clinical Investigation. 1 : 47-63.

55. CARSON, E.R., L. Finklestein, (1973).
Problems of identification in metabolic systems.
In Preprints 3rd IFAC Symposium on Identification and System Parameter Estimation. Held Delft, Holland.

56. CARSON, E.R., C. Cobelli, L. Finklestein, (1979).
The identification of metabolic systems ; a review.
In Preprints 5th IFAC Symposium on Identification and System Parameter Estimation. Held at Darmstadt, Federal Republic of Germany.

57. CERRETELLI, P., J.C. Cruz, L.E. Farhi, H. Rahn. (1966).
Determination of mixed venous O_2 and CO_2 tensions and cardiac output by a rebreathing method.
Repiration Physiology. 1 : 258-264.

58. CHANG, H.K., L.E. Farhi, (1973).
On mathematical analysis of gas transport in the lung.
Respiration Physiology. 18 : 370-385.

59 CHATFIELD, C. (1975).
Statistics for technology.
Chapman Hall, London, England.

60. CHERNIACK, N.S., G.S. Longobardo, I. Shaw, M. Heymann (1966).
Dynamics of carbon dioxide changes following an alteration in ventilation.
Journal of Applied Physiology. 21 : 785-793.

61. CHILTON, A.B., R.W. Stacy, (1952).
A mathematical analysis of carbon dioxide respiration in man.
Bulletin Mathematical Biophysics, 14 : 1-18.

62. CLARKE, D.W., (1974).
Identification package for a PDP-11 computer.
Oxford University Engineering Laboratory Report, No. 1113/74.

63. CLARKE, D.W. (1975).
Time-domain techniques of system identification.
Applications lecture No. 2. Presented at S.R.C. Vacation School on Stochastic processes in control systems.
Held at Warwick, England.

64. CLARKE, D.W., P.J. Gawthrop, (1975).
Self-tuning controller.
Proceedings I.E.E. (Control and Science), 122 : 929-934.

65. COLLIER, C.R., (1956).
Determination of mixed venous CO_2 tensions by rebreathing.
Journal of Applied Physiology, 9 : 25-29.

66. COBELLI, C., M. Frezza, C. Timbelli, (1975).
Modelling, identification and parameter estimation of bilirubin kinetics in normal, hemolytic and Gibert's states.
Computers and Biomedical Research. 8 : 522-537.

67. COBELLI, C., A. Lepschy, G. Romanin-Jacur, (1978),
Comments on "On the relationship between structural identifiability and controllability, observability properties".
I.E.E.E. Transactions Automatic Control. 23 : 965-966.

68. COBELLI, C., A. Lepschy, G. Romanin-Jacur, (1979).
Identifiability of compartmental systems and related structural properties.
Mathematical Biosciences. 44 : 1-18.

69. COBELLI, C., G. Romanin-Jacur, (1975).
Structural identifiability of strongly connected biological compartmental systems.
Medical and Biological Engineering, 13 : 831-838.

70. COBELLI, C., G. Romanin-Jacur, (1976).
Identifiability of biological compartmental systems in a general input-output configuration.
Mathematical Biosciences. 30 : 139-151.

71. COBELLI, C., G. Romanin-Jacur, (1976).
Controllability, observability and structural identifiability of multi-input, multi-output biological compartmental systems.
I.E.E.E. Transactions Biomedical Engineering. 23 : 93-100.

72. CROFTON, J., A. Douglas. (1969).
Respiratory diseases, Chapter 1.
Blackwell Scientific Publications, Oxford, England.

73. CRUZ, J.C., H. Rahn, L.E. Farhi, (1969).
Mixed Venous PO_2, PCO_2, pH and cardiac output during exercise in trained subjects.
Journal of Applied Physiology, 27 : 431-434.

74. CUNNINGHAM, J.C., E.S. Petersen, (1978).
The physiology of breathing.
Prolegomena, symposium on Modelling of a biological control system : the regulation of breathing.
Held at Oxford University, Oxford, England.

75. CUMMING, G., S.G. Semple, (1973).
Disorders of the respiratory system.
Blackwell Scientific Publications, Oxford, England.

76. DAVIDSON, W.C., (1959).
Variable metric methods for minimisation.
A.E.C. (U.S.) Research and Development Report No. ANL 5990.

77. DAVIDSON, W.C.,(1968).
Variance algorithms for minimisation.
The Computer Journal, 10 : 406-410.

78. DAVIDSON, E.J. (1977).
Connectability and structural controllability of composite systems.
Automatica. 13 : 109-123.

79. DAVIES, E.E., H.L. Hahn, S.G. Spiro, R.H.T. Edwards, (1974).
A new technique for recording respiratory transients at the start of exercise.
Respiration Physiology. 20 : 69-79.

80. DEFARES, J.G. (1958).
Determination of $P_{\bar{v}}CO_2$ from the exponential CO_2 rise during rebreathing.
Journal of Applied Physiology. 13 : 159-164.

81. DELFORGE, J. (1977).
The problem of structural identifiability of a linear compartmental system : solved or not ?
Mathematical Biosciences, 36 : 119-125.

82. DELFORGE, J. (1978).
Comments on "Controllability, observability and structural identifiability of multi-input, multi-output biological compartmental systems."
I.E.E.E. Transactions Biomedical Engineering. 25 : 400-402.

83. DENNIS, J.E., J.J. More, (1977).
Quasi-Newton methods, motivation and theory.
S.I.A.M. Review. 19 : 46-89.

84. DEUTSCH, R. (1965).
Estimation theory.
Prentice Hall, New Jersey, U.S.A.

85. DILL, D.B., W.H. Forbes, (1941).
Respiratory and metabolic effects of hypothermia.
American Journal of Physiology. 132 : 685-697.

86. DISTEFANO, J.J. (1976).
Design of tracer experiments for unique identification of non-linear physiological systems.
American Journal of Physiology. 230 : 476-485.

87. DISTEFANO, J.J. (1977).
On the relationship between structural identifiability and controllability, observability properties.
I.E.E.E. Transactions Automatic Control. 22 : 652.

88. DISTEFANO, J.J., F. Mori, (1977).
Parameter identifiability and experiment design: thyroid hormone metabolism parameters.
American Journal of Physiology, Regulatory Integrative Comparative Physiology. 2 : 134-144.

89. DISTEFANO, J.J., K.C. Wilson, M. Jang, P.H. Mak, (1975).
Identification of the dynamics of thyroid hormone metabolism.
Automatica. 11 : 149-159.

90. DITTMER, D.S., R.M. Grebe (Editors).
Handbook of respiration.
W.B. Saunders, Philadelphia, and London.

91. DIXON, L.C.W., (1972).
Non-linear optimisation.
English Universities Press, London, England.

92. DIXON, L.C.W., (1972).
The choice of steplength, a crucial factor in the performance of variable metric algorithms. In Numerical Methods for non-linear Optimisation. Lootsma, F.A., (Editor).
Academic Press, London, England.

93. DRAPER, N.R., H. Smith, (1966).
Applied regression analysis.
John Wiley, New York, U.S.A.

94. EINER-JENSEN, N. (1978).
Blood-gas probes.
Presentation at Breathing Club meeting on Lung Ventilation and Perfusion : study by mass spectrometry.
Held at Royal Society of Medicine, London, England.

95. ELGERD, O.I. (1966).
Control systems theory.
McGraw-Hill, Tokyo, Japan.

96. EMERY, B., A.I. Pack, (1971).
An experimentally verified model of the gas exchanging properties of the lung.
In I.E.E. Conference Publication, No. 79, Computers for analysis and control in medical and biological research.

97. EYKHOFF, P., (1974).
System Identification.
John Wiley, New York, U.S.A.

97a. ETSYON, J., D. Chazan, M. Itzkovitz, S. Bursztein, (1975).
Estimation of cardiac output from respiratory data.
In Signal analysis and pattern recognition in biomedical engineering, Inbar, C.F. (Editor).
John Wiley, New York, U.S.A.

98. FARHI, L.E., (1967).
Elimination of inert gas by the lung.
Respiration Physiology. 3 : 1-11.

99. FARHI, L.E., P. Haab. (1967).
Mixed venous blood gas tensions and cardiac output by "bloodless" methods : recent developments and appraisal.
Respiration Physiology. 2 : 225-232.

100. FARHI, L.E., M.S. Nesarajah, A.J. Olszowka, L.A. Metitidi, A.K. Ellis, (1976).
Cardiac output determination by simple one-step rebreathing technique.
Respiration Physiology. 28 : 141-159.

101. FARHI, L.E., H. Rahn, (1955).
Gas stores in the body and the unsteady state.
Journal of Applied Physiology. 7 : 472-484.

102. FARHI, L.E., H. Rahn. (1960).
Dynamics of changes in carbon dioxide stores.
Anaethesiology. 21 : 604-614.

103. FARHI, L.E., T. Yokoyama, (1967).
Effects of $\dot{V}_A / \dot{Q}$ inequality on elimination of inert gases.
Respiration Physiology. 3 : 12-20.

104. FÉDEROV, V.V. (1972).
Theory of optimal experiments.
Academic Press, New York, U.S.A.

105. FÉDEROV, V.V. (1971).
Asymtotically optimal designs of experiments for discriminating between two rival models.
Theory of Probability and its Applications. 16 : 561-562.

106. FEINBERG, P.N., J.D. Schoeffler, (1975).
Computer optimisation methods applied to medical diagnosis.
Computers in Biomedical Research. 5 : 3-19.

107. FENN, W.O., P. Dejours, (1954).
Composition of alveolar air during breath-holding with and without prior inhalation of oxygen and carbon dioxide.
Journal of Applied Physiology. 7 : 313-319.

108. FERGUSON, D.R. (1976).
Private communication.

109. FERGUSON, R.J., J.A. Faulkner, S. Julius, J. Conway (1968).
Comparison of cardiac output determined by CO_2 rebreathing and dye-dilution methods.
Journal of Applied Physiology. 25 : 450-454.

110. FISHMAN, A.P., H.W. Frits Jnr., A. Cournand, (1960).
Effects of breathing carbon dioxide upon the pulmonary circulation.
Circulation. 22 : 220 - 225.

111. FLETCHER, R. (1969).
A review of methods for unconstrained optimisation.
In Optimisation. Fletcher, R. (Editor).
Academic Press, New York, U.S.A.

112. FLETCHER, R. (1970).
A new approach to variable metric algorithms.
Computer Journal. 13 : 317-322.

113. FLETCHER, R. (1971).
A modified Marquandt sub-routine for non-linear least squares.
United Kingdom Atomic Energy Authority Research Group Report R-6799.

114. FLETCHER, R., M.J.D. Powell, (1963).
A rapidly convergent descent method for-function minimisation.
Computer Journal. 6 : 163-168.

115. FLETCHER, R., M.J.D. Powell, (1974).
On the modification of LDL^T factorisations.
Mathematics of Computation. 28 : 1067-1087.

116. FLETCHER, R., C.M. Reeves, (1964).
Function minimisation by conjugate gradients.
Computer Journal. 7 : 149-154.

117. FOWLE, A.S.E., E.S.M. Campbell, (1964).
The immediate carbon dioxide storage capacity of man.
Clinical Science. 27 : 41-49.

118. FOWLER, W.S. (1948).
Lung function studies II. The respiratory dead space.
American Journal of Physiology. 154 : 405-416.

119. FOWLER, W.S. (1951).
Intrapulmonary distribution of inspired gas.
Physiological Review. 32 : 1-20.

120. FOWLER, W.S., E.R. Cornish Jnr., S.S. Kety (1952).
Lung function studies VIII. Analysis of alveolar ventilation by pulmonary N_2 clearance curves.
Journal of Clinical Investigation. 31 : 40 -50.

121. FOWLER, K.T. (1969).
The respiratory mass spectrometer.
Physics in Medicine and Biology. 14 : 185-199.

122. FRANCIOSA, J.A., D.O. Ragan, S.J. Rubenstone, (1976).
Validation of the CO_2 rebreathing method for measuring cardiac output in patients with hypertension or heart failure.
Journal of Laboratory and Clinical Medicine. 88 : 672-682.

123. GILL, P.E., W. Murray, (1972).
Quasi-Newton methods for unconstrained optimisation.
Journal of the Institute of Mathematics and its Applications. 9 : 91-108.

123a. GILL, P.E., W. Murray. (1974).
Newton-type methods for unconstrained and linearly constrained optimisation.
Mathematical Programming 7 : 311-350.

124. GILL , P.E., W. Murray, (1976).
Algorithms for the solution of the non-linear least-squares problem.
National Physical Laboratory Report. No. NAC 71.

125. GILL, P.E., W. Murray, R.A. Pitfield. (1972).
The implementation of two revised Quasi-Newton methods for function minimisation.
National Physical Laboratory Report, No. NAC 11.

126. GODFREY, K.R. (1978).
Basic Statistical Theory.
Lecture No. 4. Presented at S.R.C. Vacation School on Stochastic processes in control systems.
Held at Warwick University, Warwick, England.

127. GODFREY, S., E. Wolfe, (1972).
An evaluation of rebreathing methods for measuring mixed venous PCO_2 during exercise.
Clinical Science. 42 : 345-353.

128. GOLDEN, J.F. (1972).
Mathematical modelling of pulmonary airway dynamics.
Ph.D. thesis, Rice University, Houston, U.S.A.

129. GOLDEN, J.F., J.W. Clark, P.M. Stevens, (1973).
Mathematical modelling of pulmonary airway dynamics.
I.E.E.E. Transactions Biomedical Engineering, 22 : 397-404.

130 GOLDFARB, D. (1970).
A family of variable metric methods derived by variational means.
Mathematics of Computation. 24 : 23-26.

131. GOLDFARB, D. (1976).
Factorised variable metric methods for unconstrained optimisation.
Mathematics of Computation. 30 : 796-811.

132. GOMEZ, D.M. (1963).
A mathematical treatment of the distribution of tidal volume throughout the lung.
Proceedings National Academy of Science. U.S.A. 49: 312-319.

133. GOODWIN, G.C. (1969).
Input synthesis for minimum covariance state and parameter estimation.
Electronics Letters. 5 : 539-540.

134. GOODWIN, G.C. (1971).
Optimal input signals for non-linear system identification.
Proceedings I.E.E. 118 : 922-926.

135. GOODWIN, G.C., J.C. Murdoch, R.L. Payne, (1973).
Optimal test signal design for linear single input-single output system identification.
International Journal of Control. 17 : 45-55.

136. GOODWIN, G.C., R.L. Payne, (1973).
Design and characterisation of optimal test signals for linear single input-single output parameter estimation.
In Preprints of 3rd IFAC Symposium on Identification and System Parameter Estimation.
Held at Delft, Holland.

137. GOODWIN, G.C., R.L. Payne, (1977).
Dynamic system identification : experiment design and data analysis.
Academic Press, New York, U.S.A.

138. GOODWIN, G.C., M.B. Zarrop, R.L. Payne, (1974).
Coupled design of test signals, sampling intervals and filters for system identification.
I.E.E.E. Transactions Automatic Control. 19 : 748-752.

139. GRAY, W.M. (1978).
Private communication.

140. GREER, W. (1978).
A simulation of the control of breathing in humans incorporating a structural model of the controller.
Ph.D. Thesis, University of Strathclyde, Glasgow, Scotland.

141. GREWAL, M.S., K. Glover. (1976).
Identifiability of linear and non-linear control systems.
I.E.E.E. Transactions Automatic Control. 21 : 833-837.

142. GRODINS, F.S. (1963).
Control theory and biological systems.
Columbia University Press, New York, U.S.A.

143. GRODINS, F.S., J.S. Gray, K.R. Schroeder, A.L. Norris, R.W. Jones, (1954).
Respiratory responses to CO_2 inhalation : a theoretical study of a non-linear biological regulator.
Journal of Applied Physiology. 7 : 283-308.

144. GROLLMAN, A. (1929).
The determination of the cardiac output of man by the use of acetylene.
American Journal of Physiology. 88 : 432-445.

145. GUSTAVSSON, I. (1972).
Comparison of different methods for the identification of industrial processes.
Automatica. 8 : 127-142.

146. GUSTAVSSON, I. (1973).
Survey of applications of identification in chemical and physical processes.
In Preprints 3rd IFAC Symposium on Identification and System Parameter Estimation.
Held at Delft, Holland.

147. GUSTAVSSON, I., L. Ljung, T. Soderstrom, (1976).
Identification of processes in closed loop - identifiability and accuracy aspects.
In Preprints 4th IFAC Symposium on Identification and System Parameter Estimation.
Held at Tblisi, U.S.S.R.

148. HAMILTON, W.F. (1962).
Measurement of cardiac output.
In Handbook of physiology, section 2 : circulation, Vol. I.
Hamilton, W.F. , P. Dow, (Editors).
American Physiological Society, Washington, D.C., U.S.A.

149. HANSON, R.J. , C.L. Lawson, (1969).
Extensions and applications of the Householder algorithm for solving linear least squares problems.
Mathematics of Computation. 23 : 787-812.

150. HASHIMOTO, T., A.C. Young, C.J. Martin, (1967).
Compartmental analysis of the distribution of gas in the lungs.
Journal of Applied Physiology. 23 : 203-209.

151. HARRISON, P.J. (1965).
Short-term sales forecasting.
Applied Statistics. 14 : 102.

152. HARTLEY, H.O., (1961).
The modified Gauss-Newton method for the fitting of non-linear regression functions by least squares.
Technometrics. 3 : 269-280.

153. HESTENES, M.R., E. Stiefel, (1952).
Methods of conjugate gradients for solving linear systems
Journal Research N.B.S. 49 : 409.

154. HLASTALA, M.P. (1972).
A model of fluctuating alveolar gas exchange during the respiratory cycle.
Respiration Physiology. 15 : 214-232.

155. HOMER, L.D., B. Denysyk. (1975).
Estimation of cardiac output by analysis of respiratory gas exchange.
Journal of Applied Physiology. 39 : 159-165.

156. HSIA, T.C. (1977).
System identification.
Lexington Books.

157. HUANG, H.Y. (1970).
Unified approach to quadratically convergent algorithms for function minimisation.
Journal of Optimisation Theory and its Applications. 5 : 405-423.

158. HUGHES, M.T.G. (1978).
Optimum estimation techniques.
Lecture No. 6, Presented at S.R.C. Vacation School on Stochastic processes in control systems, held at Warwick University, Warwick, England.

159. HUNTER, W.G., W.J. Hill, T.L. Henson, (1969).
Designing experiments for precise estimation of all or some of the constants in a mechanistic model.
The Canadian Journal of Chemical Engineering. 47 : 76-80.

160. INBAR, G.F., T.C. Hsia, R.J. Baskin, (1970).
Parameter identification analysis of muscle dynamics.
Mathematical Biosciences. 7 : 61-79.

161. INOUE, K., K. Ogino, Y. Savargi (1970).
Sensitivity synthesis of optimal input for parameter identification.
In Preprints 2nd. IFAC Symposium on Identification and Process Parameter estimation.
Held at Prague, Czechoslavakia.

162. ISERMANN, R., U. Bauer, W. Bamberger, P. Knepo, H. Sieberg. (1974).
Comparison of six on-line identification and parameter estimation methods.
Automatica, 10 : 81-103.

163. JALIWALA, S.A., R.E. Mates, F.J. Klocke. (1975).
An efficient optimisation technique for recovering ventilation -perfusion distributions from inert gas data.
Journal of Clinical Investigation. 55 : 188-192.

164. JENERUS, R., G. Lundin, D. Thompson. (1963).
Cardiac output in healthy subjects determined with a CO_2 rebreathing method.
Acta Physiologica Scandanavia. 59 : 300-399.

165. JONES, N.L., E.J.M. Campbell, G.T.R. McHardy, B.E. Higgs, M. Clode. (1967).
The estimation of carbon dioxide pressure of mixed venous blood during exercise.
Clinical Science. 32 : 311-327.

166. KABAILA, P.V. (1978).
Ph.D. Thesis, University of Newcastle, New South Wales, Australia.

167. KAJIYA, F., K. Kawagoe, S. Kodama, N. Hoki, M. Inoue,(1969).
A method of study of radioactive tracer kinetics.
I.E.E.E. Transactions Biomedical Engineering. 26 : 422-428.

168. KARPLUS, W.J. (1978).
The spectrum of mathematical modelling and systems simulation.
In Simulation of Systems. Dekker, L. (Editor).
North Holland.

169. KAUFMAN, R.D., K. Agleh, O. Brouko, J.W. Bellville, (1978).
Site of action of doxapram.
In Preprints of Symposium on Modelling of a biological control system : the regulation of breathing.
Held at Oxford University, Oxford, England.

170. KELMAN, G.R. (1966).
Digital computer subroutine for the conversion of oxygen tension into saturation.
Journal of Applied Physiology. 21 : 1375-1376.

171. KELMAN, G.R. (1967).
Digital computer procedure for conversion of PCO_2 into blood CO_2 content.
Respiration Physiology. 3 : 111-115.

172. KELMAN, G.R. (1972).
Errors in Riley analysis.
British Journal Anaesthesia. 44 : 433-436.

173. KETY, S.S. (1951).
The theory and applications of the exchange of inert gases at the lungs and tissues.
Pharmacological Reviews. 3 : 1- 41.

174. KEVICZKY, L., C.S. Banyasz. (1973).
On input signal synthesis for linear discrete-time systems.
In Preprints 3rd IFAC Symposium on System Identification and System Parameter Estimation.
Held at Delft, Holland.

175. KIM. T.S., H. Rahn, L.E. Farhi, (1972).
Estimation of true venous and arterial PCO_2 by gas analysis of a single breath.
Journal of Applied Physiology. 21 : 1338-1344.

176. KINNE, F. (1972).
Mass transfer in the human respiratory system.
Ph.D. Thesis, Iowa State University, Iowa, U.S.A.

177. KNOWLES, J.H., W. Newman, W.O. Fenn, (1960).
Determination of oxygenated mixed venous blood CO_2 tension by a breath-holding method.
Journal of Applied Physiology. 15 : 225-228.

178. KOOPMANS, T.C. (1949).
Identification problems in economic model construction.
Econometrika. 17 : 627-634.

179. KULLBACK, S. (1959).
Information theory and statistics.
John Wiley, New York, U.S.A.

180. LAM, C.F., A.P. Gross. (1979).
Comparitive study of parameter estimation procedures in enzymic kinetics.
Computers in Biomedical Research. 9 : 145-153.

181. LENFANT, C., T. Okubo. (1968).
Distribution function of pulmonary blood flow and ventilation - perfusion ratio in man.
Journal of Applied Physiology. 24 : 668-677.

182. LEVADI, V.S. (1966).
Design of input signals for parameter estimation.
I.E.E.E. Transactions Automatic Control. 11 : 205-211.

183. LEVENBERG, K. (1944).
A method for the solution of certain non-linear problems in least squares.
Quarterly Journal of Applied Mathematics. 2 : 164-168.

184. LEVIN, M.J. (1960).
Optimal estimation of impulse response in the presence of noise.
I.R.E. Transactions Circuit Theory. 7 : 50-56.

185. LIN, K.H., G. Cumming. (1973).
A model of time-varying gas exchange in the human lung during a respiratory cycle at rest.
Respiration Physiology. 17 : 93-112.

186. LINDLEY, D.V., A.F.M. Smith. (1972).
Bayes estimates for the linear model.
Journal Royal Statistical Society. B34 : 1-41.

187. Litman, S., W.H. Huggins. (1963).
Growing exponentials as a probing signal for system identification.
Proceedings I.E.E.E.. 51 : 917-923.

188. LJUNG. L. (1974).
Convergence of recursive stochastic algorithms.
Lund Institute of Technology, Sweden, Division of Automatic Control Report No. 7403.

189. LJUNG, L. (1977).
Analysis of recursive stochastic algorithms.
I.E.E.E. Transactions Automatic Control. 22 : 551-575.

190. LJUNG, L. (1979).
Asymtotic behaviour of the extended Kalman filter as a parameter estimator for linear systems.
I.E.E.E. Transactions Automatic Control. 24 : 36-50.

191. LJUNG, L., I. Gustavsson, T. Soderstrom. (1974).
Identification of linear multi-variable systems operating under linear feedback control.
I.E.E.E. Transactions Automatic Control. 19 : 836-840.

192. LJUNG, L., M. Morf, D. Falconer. (1978).
Fast calculation of gain matrices for recursive estimation schemes.
International Journal of Control. 27 : 1-19.

193. LONGOBARDO, G.S., N.S. Cherniack, I. Shaw. (1967).
Transients in carbon dioxide stores.
I.E.E.E. Transactions Biomedical Engineering. 14 : 182-191.

194. LOUGHMAN, J. (1973).
Cardiac output measurements by thermal dilution in anaesthesia and intensive care.
Anaesthesia and Intensive Care. 1 : 393-399.

195. MACLAINE, C.G. (1975).
An application of discrete models to the study of the mammalian muscle spindle.
Ph.D. Thesis, University of Glasgow, Glasgow, Scotland.

196. MACLAINE, C.G., P.N. McWilliam, D.J. Murray-Smith, J.R. Rosenberg. (1977).
A possible mode of action of static fusimotor axons as revealed by system identification techniques.
Brain Research. 135 : 351-357.

197. MALONEY, J., G.A. Bakey, (1976).
On-line estimation of cardiac output from respiratory measurements using a gradient method.
Medical and Biological Engineering. 14 : 379-386.

198. MANCINI, P., A. Pilo, (1970).
A computer program for multi-exponential fitting by the peeling method.
Computers and Biomedical Research. 3 : 1-14.

199. MANNARD, A., R.B. Stein. (1973).
Determination of the frequency response of isometric soleus muscle in the cat using random nerve stimulation.
Journal of Physiology. 229 : 275-296.

200. MAPLESON, W.W. (1963).
An electric analogue for uptake and exchange of inert gases and other agents.
Journal of Applied Physiology. 18 : 197-204.

201. MAPLESON, W.W. (1973).
Circulation time models of the uptake of inhaled anaesthetics and data for quantifying them.
British Journal of Anaesthesia. 45 : 319-333.

202. MARMARELIS, P., K.I. Naka. (1974).
Identification of multi-input biological signals.
I. E.E.E. Transactions Biomedical Engineering. 21 : 88-101.

203. MARQUARDT, D.W. (1963).
An algorithm for least squares estimation of non-linear parameters.
Journal of Society for Industrial and Applied Mathematics.
11 : 431-444.

204. MATALON, S.V., P.J. Manning, B.J. Berne, B.C. Eichorst, C.E. Hunt, A.E. Seeds. (1978).
The effects of changes in maternal P_{aO_2} and P_{aCO_2} on the fetal P_{aO_2} and P_{aCO_2} - in vivo study.
Respiration Physiology. 32 : 51-61.

204a. McCORMICK, G.P., J.D. Pearson. (1970).
Variable metric methods and unconstrained optimisation.
In optimisation. Fletcher, R. (Editor).
Academic Press, New York, U.S.A.

204b. McGREGOR, M., R.E. Donovan, N.M. Anderson. (1962).
Influence of carbon dioxide and hyperventilation on cardiac output in man.
Journal of Applied Physiology. 17 : 933-937.

205. MEHRA, R.K. (1974).
Optimal inputs for system identification.
I.E.E.E. Transactions Automatic Control. 19 : 192-200.

206. MEHRA, R.K. (1974).
Optimal input signals for parameter estimation in dynamic systems - survey and new results.
I.E.E.E. Transactions. Automatic Control. 19 : 753-768.

207. MEYER, R.R., P.M. Roth. (1972).
Modified damped least squares : an algorithm for non-linear estimation.
Journal of the Institute of Mathematics and its Applications. 9 : 218-233.

208. MILANESE, M., G.P. Molino. (1975).
Structural identifiability of compartmental models and patho-physiological information from the kinetics of drugs.
Mathematical Biosciences. 26 : 175-190.

209. MILIC-EMILI, J.J., A.M. Henderson, M.B. Dolovich, D. Trop, K. Kaneko. (1966).
Regional distribution of inspired gas in the lung.
Journal of Applied Physiology. 21 : 749-759.

210. MILLHORN, H.T. (1966).
The application of Control Theory to physiological systems.
W.B. Saunders Company, Philadelphia, U.S.A.

211. MOLINO, G.P., M. Milanese. (1975).
Structural analysis of compartmental models for the hepatic kinetics of drugs.
Journal of Laboratory and Clinical Medicine. 85 : 865-878.

212. MURPHY, T.W. (1969).
Modelling of lung gas exchange - mathematical models of the lung ; the Bohr model, static and dynamic approaches.
Mathematical Biosciences. 5 : 427-447.

213. MURRAY, W. (1977).
Algorithms for static optimisation I.
Lecture No. 3. S.R.C Vacation School on Systems modelling and optimisation.
Held at Cambridge University, Cambridge, England.

214. MURRAY-SMITH, D.J., A.I. Pack, (1977).
Techniques of computer simulation applied to respiratory gas exchange.
In Non-invasive clinical measurements. Taylor, D.C., J. Whamond, (Editors). Pitman Medical.

215. MURTAGH, B.A., R. W.H. Sargent, (1969).
A constrained minimisation method with quadratic convergence.
In Optimisation. Fletcher, R. (Editor).
Academic Press, New York, U.S.A.

216. NAHI, N.E., G.A. Napjus, (1971).
Design of optimal probing signals for vector parameter estimation.
In Preprints I.E.E.E. Conference on Decision and control.
Held at Miami, Florida, U.S.A.

217. NAKAMURA, T., T. Takishima, T. Okubo, T. Sasaki, H. Takahashi. (1966).
Distribution function of the clearance time constant in lungs.
Journal of Applied Physiology. 21 : 227-232.

218. NEYMAN, J., E.S. Pearson, (1928).
On the use and interpretation of certain test criteria for the purposes of statistical inference.
Biometrika. 20A : 175-263.

219. NG., T.S., G.C. Goodwin, (1976).
On optimal choice of sampling strategies for linear system identification.
International Journal of Control. 23 : 459-475.

220. NOTON, M. (1972)
Computer algorithms for model fitting.
In Chemical Engineers Symposium Series, No. 35.
Institute of Chemical Engineers, London, England.

221. NUNN, J.F. (1969).
Applied respiratory physiology.
Butterworths, London, England.

222. NYE, R.E. (1970).
Influence of the cyclical pattern of ventilatory flow on pulmonary gas exchange.
Respiration Physiology. 10 : 321-337.

223. OHTSU, K., M. Horigome, G. Kitagawa, (1979).
A new ship's auto-pilot design through a stochastic model.
Automatica. 15 : 255-268.

224. OKUBO, T., C. Lenfant, (1968).
Distribution function of lung volume and ventilation determined by lung N_2 washout.
Journal of Applied Physiology. 24 : 658-667.

225. OLSZOWKA, A.J. (1975).
Can $\dot{V}_A/\dot{Q}$ distribution in the lung be recovered from inert gas retention data ?
Respiration Physiology. 25 : 191-198.

226. OLSSON, G. (1973).
Modelling and identification of nuclear power reactor dynamics from multi-variable experiments.
In Preprints 3rd. IFAC Symposium on Identification and System Parameter Estimation.
Held at Delft, Holland.

227. OOTOMO, T., T. Nakagawa, H. Akaike, (1972).
Statistical approach to computer control of a cement rotary kiln.
Automatica, 8 : 35-48.

228. PACK, A.I. (1976).
Mathematical models of lung function.
Ph.D. Thesis, *University of Glasgow, Glasgow, Scotland.*

229. PACK, A.I., B. Emery, F. Moran, D.J. Murray-Smith, (1974).
Computer models of gas exchange processes in pulmonary ventilation.
In Ventilatory and phonatory control systems. Wyke, B. (Editor), Oxford University Press, London, England.

230. PACK, A.I., D.J. Murray-Smith, (1972).
Mathematical models and their applications in medicine.
Scottish Medical Journal. 17 : 401-409.

231. PACK, A.I., W. Nixon, M. Hooper, J.C. Taylor, (1977).
A computational model of pulmonary gas transport incorporating effective diffusion.
Respiration Physiology. 29 : 101-124.

232. PAPPENHEIMER, J. et al. (1950).
Standardisation of definitions and symbols in respiratory physiology.
Federation Proceedings. 9 : 602-605.

233. PAYNE, R.L., G.C. Goodwin, M.B. Zarrop. (1975).
Frequency domain approach for designing sampling rates for system identification.
Automatica, 11 : 189-193.

234. PEARSON, K.G. (1975).
Parameter estimation techniques applied to a model of human respiratory gas exchange processes.
Ph.D. Thesis, University of Glasgow, Glasgow, Scotland.

235 PESLIN, R., S. Dawson, J. Mead. (1971).
Analysis of multi-component exponential curves by the Post-Widders equation.
Journal of Applied Physiology, 30 : 462-472.

236. PESLIN, R., J. Papon, C. Duviver, J. Richalet, (1975).
Frequency response of the chest : modelling and parameter estimation.
Journal of Applied Physiology. 39 : 523-524.

237. PETERS, J.P., H.A. Bulger, A.J. Eisenman, (1924).
Studies of the carbon dioxide absorption of human blood IV.
The relation of the haemoglobin content of the blood to the form of the carbon dioxide absorption curve.
Journal of Biological Chemistry, 58: 747-768.

238. PIIPER, J., P. Dejours, P. Haab, H. Rahn. (1971).
Concepts and basic quantities in gas exchange physiology.
Respiration Physiology, 13 : 293-304.

239. POULIQUEN, R., J. Estapa, J. Richalet, (1968).
Identification by frequency methods and sensitivity functions.
In Preprints 2nd. IFAC Symposium on System Sensitivity and Adaptivity. Held at Dubrovnick, Yugoslavia.

240. POWELL, M.J.D., (1964).
An efficient method for finding the minimum of a function of several variables without calculating derivatives.
Computer Journal, 7 : 155-162.

241. RAULT, A., (1973).
Identification applications to aeronautics.
In Preprints 3rd. IFAC Symposium on Identification and System Parameter Estimation.
Held at Delft, Holland.

242. RAULT, A., R. Pouliquen, J. Richalet, (1969).
Sensibilizing input and identification.
In Preprints 4th IFAC Congress.
Held at Warsaw, Poland.

243. REYBROUCK, T., A. Amery, L. Billiet, R. Fagard, H. H. Stijns, (1978).
Comparison of cardiac output determined by a carbon dioxide -rebreathing and direct Fick method at rest and during exercise.
Clinical Science and Molecular Medicine. 55 : 445-452.

244. RIGGS, D.S. (1970).
Control theory and physiological feedback mechanisms.
The Williams and Wilkins Company. Baltimore, U.S.A.

245. RILEY, R.L., A. Cournand. (1949).
'Ideal' alveolar air and the analysis of ventilation-perfusion relationships in the lungs.
Journal of Applied Physiology. 1 : 825-847.

246. RILEY, R.L., A. Cournand. (1951).
Analysis of factors affecting partial pressures of oxygen and carbon dioxide in gas and blood of lungs. : theory.
Journal of Applied Physiology. 4 : 77-101.

247. ROBERTSON, J.S., W.E. Siri, H.B. Jones. (1950).
Lung ventilation patterns determined by analysis of nitrogen elimination rates : use of the mass spectrometer as a continuous gas analyser.
Journal of Clinical Investigation. 29 : 577-590.

248. ROCKAFELLAR, R. (1970).
Convex analysis.
Princeton University Press, New Jersey, U.S.A.

249. ROSENBROCK, H.H. (1960).
An automatic method for finding the greatest or least value of a function.
Computer Journal. 3 : 175-184.

250. ROSSING, R.G. (1970).
A comparison of rate variables for the description of the nitrogen washout curve.
Mathematical Biosciences, 6 : 283-293.

251. ROSSING, R.G., M.B. Danford, E.L. Bell, R. Gracia, (1967).
Mathematical models for the analysis of the nitrogen washout curve.
Report SAM-TR-67-100. USAF School of Aerospace Medicine Brooks, Air Force Base, Texas, U.S.A.

252. SACKNER, M.A. , D. Greenletch, M.S. Heiman, S. Epstein, N. Atkins, (1975).
Diffusing capacity, membrane diffusing capacity, capillary blood volume, pulmonary tissue volume and cardiac output measured by rebreathing technique.
American Review of Respiratory Disease. 111 : 157-165.

253. SAIDEL, G.M., T.C. Militano, E.H. Chester, (1972).
Mass balance model of pulmonary oxygen transport.
I.E.E.E. Transactions on Biomedical Engineering, 19 : 205-213.

254. SCRIMSHIRE, D.A., (1977).
Theoretical analysis of independent $\dot{V}_A$ and $\dot{Q}$ inequalities upon pulmonary gas exchange.
Respiration Physiology. 29 : 163-178.

255. SCRIMSHIRE, D.A. (1978).
Personal communication.

256. SERVINGHAUS, J.W. (1966).
Blood-gas calculator.
Journal of Applied Physiology. 21 : 1108-1116.

257. SHANNON, C.E. (1948).
A mathematical theory of communication.
Bell System Technical Journal. 27 : 379-423 and 623-656.

258. SHANNO, D.F. (1970).
Conditioning of Quasi-Newton methods for function minimisation.
Mathematics of Computation. 24 : 647-657.

259. SHEPPARD, C.W. (1962).
Basic principles of the tracer method.
John Wiley, New York, U.S.A.

260. SIKEND, R.S., H. Magnusson, P. Scheid, J. Piiper, (1976).
Convective and diffusive gas mixing in human lungs : experiments and model analysis.
Journal of Applied Physiology. 36 : 91-97.

261. SILVEY, S.D. (1975).
Statistical Inference.
Chapman,Hall, London, England.

262. SLATE, J.B., L.C. Sheppard, V.C. Rideout, E.H. Blackstone, (1979).
A model for design of a blood pressure controller for hypertensive patients.
In Preprints 5th IFAC Symposium on Identification and System Parameter Estimation.
Held at Darmstadt, Federal Republic of Germany.

263. SODERSTROM, T. (1977).
On model structure testing in system identification.
International Journal of Control. 26 : 1-18.

264. SODERSTROM, T., L. Ljung, I. Gustavsson, (1978).
A theoretical analysis of recursive identification methods.
Automatica. 14 : 231-244.

265. SPEEDY, G.B., R.F. Brown, G.C. Goodwin, (1970).
Control theory : identification and optimal control.
Oliver and Boyd, Edinburgh, Scotland.

266. STEPHENSON, G.C. (1970).
A hierarchy of models for planning in a division of I.C.I.
Operational Research Quarterly. 20 : 221-245.

267. STEWART, G.W. (1967).
A modification of Davidsons minimisation method to accept difference approximations to derivatives.
Journal of the Association for Computing Machinery. 14 : 72-83.

268. STOLL, P.J., J.S. Meditch, (1970).
Least squares estimation of respiratory system parameters.
Mathematical Biosciences. 8 : 307-321.

269. STOUT, R.L., H.U. Wessel, M.H. Paul, (1975).
Pulmonary blood flow determined by continuous analysis of pulmonary N_2O exchange.
Journal of Applied Physiology. 38 : 913-918.

270. STOREY, C. (1977).
Methods for dynamic optimisation.
Lectures No. 5, 6. S.R.C. Vacation School on Systems modelling and optimisation.
Held at Cambridge University, Cambridge, England.

271. SUWA, K., H.H. Benedixen, (1972).
Pulmonary gas transport in a tidally ventilated single alveolus model.
Journal of Applied Physiology. 32 : 834-841.

272. SWANSON, G.D. (1972).
Dynamic end-tidal forcing in the study of the human respiratory system.
Ph.D. Thesis , Stanford University, Stanford, U.S.A.

273. SWANSON, G.D. (1977).
Biological signal conditioning for system identification.
Proceedings, I.E.E.E. 65 : 735-740.

274. SWANSON, G.D. (1977).
Evaluation of the Grodins respiratory model via dynamic end-tidal forcing.
American Journal of Physiology, Regulatory Integrative Comparative Physiology, 2 : 66-72.

275. SWANSON, G.D. (1978).
Input stimulus design for model discrimination in human respiratory control.
In Preprints Symposium on Modelling of a biological control system : the regulation of breathing.
Held at Oxford University, Oxford, England.

276. SWANSON, G.D., J.W. Bellville, (1974).
Hypoxic-hypercapnic interaction in human respiratory control.
Journal of Applied Physiology. 36 : 480-487.

277. SWANSON, G.D., J.W. Bellville, (1975).
Step changes in end-tidal CO_2 : methods and implications.
Journal of Applied Physiology, 39 : 377-385.

278. SWANSON, G.D., T.M. Carpenter, D.E. Snider, J.W. Bellville, (1971).
An on-line hybrid computing system for dynamic respiratory response studies.
Computers and Biomedical Research. 4 : 205-215.

279. SWANSON, G.D., D.S. Ward, J.W. Bellville, (1976).
Posthyperventilation isocapnic hyperpnea.
Journal of Applied Physiology, 40 : 392-396.

280. SWANSON, G.D., B.J. Whipp, R.D. Kaufman, K.A. Agleh, B. Winter, J.W. Bellville, (1978).
Effect of hypercapnia on hypoxic ventilatory drive in normal and carotid body-resected man.
Journal of Applied Physiology, Respiratory Environment Exercise Physiology. 45 : 971-977.

281. TOMOVIC, R. (1963).
Sensitivity analysis of dynamic systems.
McGraw-Hill, New York, U.S.A.

282. TRUEB, T.J., N.S. Cherniack, A.F. D'Souza, A.P. Fishman, (1971).
A mathematical model of the controlled plant of the respiratory system.
Biophysics Journal, 11 : 810-834.

283. TSAI, M.J., R.L. Pimmel, P.A. Bromberg, R.B. McGee, (1977).
An evaluation of recovery of ventilation-perfusion ratios from inert gas data.
Computers and Biomedical Research. 10 : 101-112.

284. TUMEY, S.Z., W. Blumenfeld, (1973).
Heated Fleisch pneumotachometer : a calibration procedure.
Journal of Applied Physiology. 34 : 117-121.

285. VAN DER BOS, A. (1973).
Selection of periodic test signals for estimation of linear system dynamics.
In Preprints 3rd. IFAC Symposium on Identification and System Parameter Estimation.
Held at Delft, Holland.

286. VAN LIEW, H.D. (1967).
Graphic analysis of aggregates of linear and exponential processes.
Journal of Theoretical Biology. 16 : 43-53.

287. VISSER, B.F., J.G. Defares, (1962).
Annels New York Academic of Science. 96 : 939-955 (Article 4).

288. WAGNER, P.D. (1975).
Letter to the editor.
Journal of Applied Physiology. 38 : 950-953.

289. WAGNER, P.D., J.W. Evans (1977).
Conditions for equivalence of gas exchange in series and parallel models of the lung.
Respiration Physiology. 31 : 117-138.

290. WAGNER, P.D., J.W. Evans, J.B. West, (1975).
Analytically derived distributions of ventilation-perfusion ratios in chronic lung disease.
Federation Proceedings. 34 : 451.

291. WAGNER, P.D., R.B. Laravuso, R.R. Uhl, J.B. West, (1974).
Continuous distributions of ventilation-perfusion ratios in normal subjects breathing air and 100% O_2 .
Journal of Clinical Investigation. 54 : 54-68.

292. WAGNER, P.D., H.A. Saltzmann, J.B. West, (1974).
Measurement of continuous distributions of ventilation-perfusion ratios : theory.
Journal of Applied Physiology, 36 : 588-599.

293. WELLSTEAD, P.E., P. Zanker, (1978).
The techniques of self-tuning.
University of Manchester Institute of Science and Technology, Control Systems Centre Report, No. 432.

294. WEST, J.B. (1976).
Ventilation/blood flow and gas exchange.
Blackwell Scientific Publications, Oxford, England.

295. WEST, J.B., C.T. Dollery, (1960).
Distribution of blood flow - ventilation - perfusion ratio in the lung measured with radioactive CO_2 .
Journal of Applied Physiology. 15 : 405-410.

296. WIBERG, D.M., J.W. Bellville, O. Brovko, R. Maine, T.C. Tai, (1979).
Modelling and parameter identification of the human respiratory system.
In Proceedings 1978 I.E.E.E. Conference on Decision and Control (including the 17th Symposium on Adaptive Processes :) 1313-1318, I.E.E.E., New York, U.S.A.

297. WILKINSON, J.H., C. Reinch, (1971).
Linear algebra.
Springer-Verlag, Berlin and New York.

298. WILSON, K.C., M. Jang, P.H. Mak, J.J. Distefano, (1973).
Identification of the dynamics of thyroid hormone binding, distribution and disposal.
In Preprints 3rd IFAC Symposium on Identification and System Parameter Estimation.
Held at Delft, Holland.

299. WITTENMARK, B. (1975).
Stochastic adaptive control methods : a survey.
International Journal of Control. 21 : 705-730.

300. WOLFE, P. (1978).
Numerical methods for unconstrained optimisation.
Van Nostrand-Reinhold, San Francisco, U.S.A.

301. YAMAMOTO, W.S. (1960).
Mathematical analysis of the time-course of alveolar CO_2 .
Journal of Applied Physiology. 15 : 215-219.

302. YAMAMOTO, W.S., T. Hori, (1971).
Phasic air movement model of respiratory regulation of carbon dioxide balance.
Computers and Biomedical Research. 3 : 699 - 717.

303. YAMAMOTO, W.S., W.F. Raub. (1967).
Models of the regulation of external respiration in mammals : problems and promises.
Computers and Biomedical Research. 1 : 65-104.

304. YAMASHIRO, S., J. Maloney, J.A. Daubenspeck, S.K. Karuza, (1975).
Estimation of human lung clearance dynamics by pseudo-random binary testing.
In Proceedings 8th Hawaii Conference on System Science: 169-170.

305. YOKOYAMA, T., L.E. Farhi, (1967).
Study of ventilation-perfusion ratio distribution in the anaesthetized dog multiple inert gas washout.
Respiration Physiology. 3 : 166-176.

306. ZADEH, L.A. (1962).
From circuit theory to system theory.
Proceedings, I.R.E. 50 : 856-865.

307. ZAZWORSKY, R.M., H.K. Knudsen, (1977).
Comments on "Controllability, observability and structural identifiability of multi input and multi output biological compartmental systems".
I.E.E.E. Transactions Biomedical Engineering, 24 : 495-496.

308. ZEIDIFARD, E., S. Godfrey, E.E. Davies, (1976).
Estimation of cardiac output by an N_2O rebreathing method in adults and children.
Journal of Applied Physiology. 41 : 433-438.

309. ZWART, A., R.C. Seagrave, A. Van Dieren, (1976).
Ventilation-perfusion ratio obtained by a non-invasive frequency response technique.
Journal of Applied Physiology. 41 : 419-424.

310. ZWART, A., N.T. Smith, J.E.W. Beneken, (1972).
Multiple model approach to uptake and distribution of halothane : the use of an analog computer.
Computers and Biomedical Research. 5 : 228-238.

APPENDICES

APPENDIX A

A1. VALIDATION DATA

Estimation Results

Four Parameters

FILE	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$\Sigma e^2_{i/m}$
VAL041	6.45 ± 0.12	1.85 ± 0.07	0.265 ± 0.0013	7.18 ± 0.18	0.0276
2	6.36 ± 0.06	1.73 ± 0.12	0.237 ± 0.0025	9.21 ± 0.68	0.1010
3	6.29 ± 0.23	1.92 ± 0.11	0.262 ± 0.0028	11.8 ± 0.96	0.0848
4	5.87 ± 0.24	1.62 ± 0.14	0.213 ± 0.0022	7.70 ± 0.54	0.0885
VAL051	6.84 ± 0.34	2.54 ± 0.26	0.300 ± 0.0036	13.1 ± 1.97	0.0800
2	5.58 ± 0.45	2.66 ± 0.28	0.295 ± 0.0050	8.76 ± 1.37	0.1430
3	7.10 ± 0.27	3.05 ± 0.19	0.334 ± 0.0032	10.1 ± 0.70	0.0504
VAL072	6.89 ± 0.33	1.36 ± 0.16	0.244 ± 0.0020	4.87 ± 0.22	0.0597
3	—				
4	6.50 ± 0.38	1.39 ± 0.05	0.218 ± 0.0020	4.04 ± 0.24	0.0773
VAL081	5.16 ± 0.17	0.96 ± 0.15	0.185 ± 0.0026	5.15 ± 0.37	0.0948
4	5.94 ± 0.45	2.34 ± 0.55	0.208 ± 0.0034	6.66 ± 1.01	0.0744
5	5.97 ± 0.26	0.98 ± 0.19	0.207 ± 0.0023	4.94 ± 0.44	0.0706
VAL101	8.23 ± 0.32	2.22 ± 0.16	0.310 ± 0.0042	10.9 ± 0.70	0.0921
2	7.66 ± 0.35	1.58 ± 0.19	0.277 ± 0.0031	7.23 ± 0.40	0.0909
3	7.40 ± 0.35	1.92 ± 0.20	0.276 ± 0.0039	8.35 ± 0.50	0.1100
4	7.38 ± 0.61	1.91 ± 0.26	0.328 ± 0.0095	10.4 ± 1.01	0.2450
VAL111	5.63 ± 0.34	2.66 ± 0.22	0.272 ± 0.0031	7.49 ± 0.64	0.1050
2	5.44 ± 0.39	2.26 ± 0.33	0.277 ± 0.0051	10.2 ± 1.47	0.0959
3	7.79 ± 0.56	2.39 ± 0.32	0.302 ± 0.0053	9.11 ± 0.79	0.0881
4	8.58 ± 0.76	1.40 ± 0.38	0.258 ± 0.0051	6.02 ± 0.42	0.1720
VAL122	4.21 ± 0.22	1.63 ± 0.14	0.210 ± 0.0031	4.59 ± 0.29	0.1490
3	—				
4	3.13 ± 0.49	2.03 ± 0.33	0.187 ± 0.0052	2.87 ± 0.37	0.3820
5	4.50 ± 0.19	1.80 ± 0.10	0.237 ± 0.0028	4.46 ± 0.28	0.1640
VAL141	7.30 ± 0.27	2.18 ± 0.15	0.361 ± 0.0037	8.94 ± 0.51	0.0980
2	6.34 ± 0.20	1.42 ± 0.13	0.266 ± 0.0025	6.83 ± 0.34	0.0654
3	—				
4	5.86 ± 0.30	1.84 ± 0.17	0.264 ± 0.0031	5.38 ± 0.33	0.1090
VAL161	6.93 ± 0.80	2.36 ± 0.51	0.261 ± 0.0069	5.93 ± 1.04	0.4010
2	5.94 ± 0.50	1.29 ± 0.26	0.209 ± 0.0029	3.73 ± 0.34	0.1290
3	5.68 ± 0.64	3.66 ± 0.47	0.259 ± 0.0066	7.73 ± 2.03	0.3240
4	6.48 ± 0.46	2.73 ± 0.29	0.275 ± 0.0048	7.47 ± 0.84	0.1340
VAL172	5.13 ± 0.47	1.68 ± 0.21	0.242 ± 0.0025	2.31 ± 0.18	0.1770
3	6.71 ± 0.61	3.43 ± 0.42	0.288 ± 0.0035	6.62 ± 1.13	0.2320
4	4.92 ± 0.29	1.48 ± 0.18	0.237 ± 0.0024	4.11 ± 0.29	0.0995

cont'd.....

APPENDIX A.1 Cont'd.....

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$\Sigma e_{i/m}^2$
VAL181	4.73 ± 0.31	1.58 ± 0.13	0.234 ± 0.0035	4.11 ± 0.27	0.0773
3	4.98 ± 0.32	1.73 ± 0.18	0.255 ± 0.0043	5.34 ± 0.37	0.1390
4	4.46 ± 0.27	1.41 ± 0.14	0.234 ± 0.0028	4.00 ± 0.23	0.1050
VAL191	3.78 ± 0.18	1.26 ± 0.13	0.182 ± 0.0023	3.96 ± 0.31	0.1070
VAL203	6.40 ± 0.39	1.65 ± 0.19	0.259 ± 0.0035	5.10 ± 0.27	0.1270
VAL221	5.70 ± 0.19	2.16 ± 0.12	0.294 ± 0.0027	9.11 ± 0.61	0.0961
2	5.78 ± 0.21	2.03 ± 0.12	0.263 ± 0.0022	6.08 ± 0.27	0.0733
3	5.94 ± 0.31	1.81 ± 0.17	0.255 ± 0.0029	5.53 ± 0.27	0.1410
4	5.76 ± 0.22	1.86 ± 0.11	0.247 ± 0.0020	5.24 ± 0.22	0.0741
VAL231	7.71 ± 0.38	2.99 ± 0.24	0.398 ± 0.0066	12.4 ± 1.06	0.1900
2	6.64 ± 0.35	1.82 ± 0.13	0.212 ± 0.0032	5.69 ± 0.30	0.0564
3	7.78 ± 0.35	3.26 ± 0.23	0.357 ± 0.0052	12.9 ± 1.08	0.1090
VAL251	6.46 ± 0.50	1.65 ± 0.28	0.239 ± 0.0040	6.57 ± 0.47	0.1060
2	6.19 ± 0.40	1.45 ± 0.22	0.211 ± 0.0024	4.92 ± 0.24	0.0686
3	4.79 ± 0.23	1.57 ± 0.13	0.236 ± 0.0027	5.73 ± 0.33	0.0782
4	—				

A.2 : VALIDATION DATA : ESTIMATION RESULTS : SIX PARAMETERS

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	$\sum e_i^2/m$
VAL041	6.28 ± 0.14	1.79 ± 0.07	0.245 ± 0.0082	6.22 ± 0.42	26.5 ± 0.26	35.4 ± 0.35	0.0255
2	6.17 ± 0.32	1.70 ± 0.12	0.218 ± 0.0203	8.12 ± 1.24	30.4 ± 0.59	37.2 ± 0.74	0.1010
3	6.42 ± 0.35	1.80 ± 0.09	0.274 ± 0.0456	12.1 ± 2.65	30.3 ± 0.49	34.5 ± 0.79	0.0848
4	6.48 ± 0.29	1.79 ± 0.16	0.417 ± 0.14	20.0 ± 8.91	32.9 ± 0.46	35.4 ± 0.53	0.0885
VAL051	6.94 ± 0.43	2.89 ± 0.33	0.407 ± 0.176	22.6 ± 15.1	32.0 ± 0.70	36.0 ± 1.17	0.0535
2	7.08 ± 0.41	3.26 ± 0.31	208.0 ± 0.134	1.1×10^4	30.7 ± 0.89	34.3 ± 1.52	0.0544
3	7.14 ± 0.30	2.78 ± 0.21	0.319 ± 0.033	9.33 ± 1.55	28.6 ± 0.65	34.2 ± 0.83	0.0349
VAL072	7.04 ± 0.40	1.44 ± 0.21	0.260 ± 0.0196	5.55 ± 0.86	37.6 ± 1.53	41.7 ± 0.82	0.0571
3	—						
4	6.39 ± 0.42	1.47 ± 0.21	0.220 ± 0.0107	3.96 ± 0.58	35.0 ± 1.91	43.9 ± 0.98	0.0695
VAL081	5.62 ± 0.16	1.04 ± 0.12	25.9 ± 0.0238	7.72 ± 0.997	38.3 ± 1.14	40.3 ± 0.47	0.0440
4	6.92 ± 0.69	3.61 ± 0.91	7.07 ± 252.9	$592.0 \pm 2.1 \times 10^4$	38.1 ± 0.74	39.9 ± 1.15	0.0475
5	5.92 ± 0.37	2.29 ± 0.42	1.74 ± 10.87	117.0 ± 798.3	38.7 ± 0.66	39.9 ± 0.853	0.0491
VAL101	9.10 ± 0.34	2.38 ± 0.14	0.535 ± 0.1	20.7 ± 4.67	36.5 ± 0.71	39.9 ± 0.51	0.0500
2	7.97 ± 0.36	1.87 ± 0.19	0.393 ± 0.089	13.7 ± 0.99	39.5 ± 0.99	38.9 ± 0.59	0.0563
3	7.14 ± 0.46	1.57 ± 0.15	0.214 ± 0.091	5.88 ± 1.55	35.2 ± 0.69	43.5 ± 0.91	0.0965
4	7.45 ± 0.68	1.79 ± 0.30	0.315 ± 0.095	10.0 ± 3.81	38.6 ± 1.71	40.0 ± 1.33	0.2200
VAL111	5.73 ± 0.36	2.77 ± 0.27	0.315 ± 0.0584	10.0 ± 3.70	40.1 ± 0.44	45.6 ± 0.81	0.0991
2	5.39 ± 0.38	1.54 ± 0.24	0.209 ± 0.0255	5.37 ± 1.37	40.9 ± 0.99	45.6 ± 1.23	0.122
3	6.56 ± 0.40	1.81 ± 0.16	0.203 ± 0.0119	4.85 ± 0.63	39.3 ± 0.94	44.1 ± 0.99	0.072
4	6.86 ± 0.45	1.13 ± 0.18	0.178 ± 0.0063	2.80 ± 0.27	37.9 ± 1.10	44.9 ± 0.82	0.0628
VAL122	4.12 ± 0.24	1.59 ± 0.16	0.218 ± 0.0316	4.83 ± 1.06	32.9 ± 0.71	41.5 ± 1.07	0.133
3	4.16 ± 0.22	0.989 ± 0.11	0.206 ± 0.026	4.29 ± 0.84	37.0 ± 0.77	41.2 ± 0.76	0.105
4	2.58 ± 0.26	1.20 ± 0.18	0.124 ± 0.030	0.907 ± 3.2	35.1 ± 0.69	57.6 ± 0.89	0.218
5	4.61 ± 0.20	1.90 ± 0.13	0.269 ± 0.0303	5.51 ± 1.01	37.5 ± 0.60	42.4 ± 0.87	0.150

cont'd.....

A.2 Continued .....

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	$\Sigma e_i^2 / m$
VAL141	7.06 ± 0.27	1.96 ± 0.16	0.301 ± 0.0288	7.03 ± 0.77	34.6 ± 0.82	43.1 ± 0.84	0.0805
2	6.73 ± 0.24	1.54 ± 0.14	0.348 ± 0.0415	9.53 ± 1.48	36.3 ± 0.74	41.4 ± 0.60	0.0480
3	5.66 ± 0.30	1.75 ± 0.14	0.227 ± 0.0184	4.86 ± 0.67	38.5 ± 0.88	44.7 ± 0.15	0.0989
4	5.77 ± 0.31	1.74 ± 0.17	0.259 ± 0.0216	5.21 ± 0.67	37.0 ± 0.64	43.5 ± 0.86	0.0853
VAL161	8.55	4.03	$278.0 \pm 1.2 \times 10^4$		34.3 ± 0.9	34.5 ± 1.2	0.145
2	6.64 ± 0.43	1.62 ± 0.27	0.333 ± 0.0678	8.60 ± 2.47	34.8 ± 1.12	35.7 ± 0.72	0.0606
3	6.14 ± 0.84	4.09 ± 0.78	0.387 ± 0.33	14.7 ± 19.2	32.5 ± 1.60	37.2 ± 2.98	0.307
4	7.13 ± 0.58	2.78 ± 0.31	0.353 ± 0.0597	10.5 ± 2.77	27.8 ± 1.04	34.2 ± 1.12	0.106
VAL172	5.43 ± 0.36	2.23 ± 0.23	0.368 ± 0.14	6.28 ± 2.14	35.2 ± 0.75	37.6 ± 0.88	0.0983
3	6.06 ± 0.58	3.58 ± 0.35	0.267 ± 0.0168	5.88 ± 0,95	31.6 ± 0.60	42.7 ± 1.40	0.173
4	5.00 ± 0.35	1.47 ± 0.21	0.245 ± 0.0201	4.46 ± 1.02	34.2 ± 0.77	41.6 ± 1.09	0.0984
VAL181	4.41 ± 0.24	1.43 ± 0.09	0.209 ± 0.0068	2.4 ± 0.28	30.9 ± 1.61	52.6 ± 1.30	0.0299
3	4.94 ± 0.24	1.46 ± 0.13	0.220 ± 0.0183	4.59 ± 0.59	37.6 ± 0.77	42.8 ± 0.86	0.0580
4	4.63 ± 0.29	1.45 ± 0.16	0.266 ± 0.032	5.22 ± 1.14	39.9 ± 0.82	46.1 ± 1.05	0.0916
VAL191	4.02 ± 0.22	1.27 ± 0.13	0.218 ± 0.0272	5.42 ± 1.16	40.2 ± 1.45	43.7 ± 1.07	0.0885
VAL203	6.08 ± 0.43	1.49 ± 0.17	0.222 ± 0.0148	3.81 ± 0.54	38.3 ± 0.91	46.3 ± 1.08	0.114
VAL221	5.59 ± 0.22	1.97 ± 0.12	0.251 ± 0.0227	7.24 ± 1.01	36.8 ± 0.51	43.6 ± 0.78	0.0838
2	5.71 ± 0.22	1.98 ± 0.133	0.256 ± 0.0163	5.82 ± 0.64	35.4 ± 0.41	42.7 ± 0.56	0.0696
3	5.48 ± 0.27	1.48 ± 0.11	0.194 ± 0.0099	3.69 ± 0.31	37.0 ± 0.58	43.2 ± 0.78	0.0843
4	5.96 ± 0.21	1.98 ± 0.12	0.290 ± 0.0211	6.84 ± 0.80	37.4 ± 0.38	41.1 ± 0.46	0.0574
VAL231	8.25 ± 0.39	3.46 ± 0.28	0.949 ± 0.47	33.5 ± 18.77	33.4 ± 0.76	36.9 ± 0.83	0.128
2	6.42 ± 0.45	1.93 ± 0.19	0.204 ± 0.0422	5.50 ± 1.47	30.1 ± 5.05	41.3 ± 1.80	0.0504
3	6.91 ± 0.44	2.89 ± 0.23	0.206 ± 0.0324	6.95 ± 1.20	32.3 ± 1.18	44.8 ± 1.71	0.0770
VAL251	6.89 ± 0.48	1.47 ± 0.25	0.272 ± 0.0369	8.49 ± 1.73	42.3 ± 1.01	43.3 ± 0.75	0.0668
2	6.49 ± 0.42	1.23 ± 0.25	0.215 ± 0.0169	5.27 ± 0.67	41.3 ± 1.23	43.0 ± 0.72	0.0589
3	4.75 ± 0.23	1.43 ± 0.11	0.224 ± 0.0212	5.53 ± 0.85	39.1 ± 0.56	45.0 ± 0.80	0.0494
4	—						

A.3 VALIDATION DATA

Estimation Results

Eight Parameters

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	a	b	$\Sigma e^2_{i/m}$
VAL041	6.29	1.79	0.246	6.28	26.6	35.3	0.736	0.808	0.0250
	(0.15)	(0.08)	(0.0088)	(0.44)	(0.27)	(0.37)	(0.38)	(1.40)	
2	6.40	1.72	0.234	8.87	30.7	36.6	-0.312	-0.011	0.0929
	(0.48)	(0.16)	(0.034)	(2.09)	(0.64)	(1.01)	(0.667)	(0.64)	
3	6.80	1.88	0.318	14.3	29.7	33.9	-0.429	0.201	0.0422
	(0.72)	(0.15)	(0.118)	(6.73)	(0.41)	(1.43)	(0.31)	(0.32)	
4	—								
VAL051	6.75	2.68	0.396	21.8	32.8	36.1	0.34	0.79	0.0512
	(0.55)	(0.52)	(0.26)	(21.2)	(0.8)	(1.63)	(0.75)	(0.77)	
2	—								
3	7.19	2.69	0.313	9.04	28.6	34.2	-0.153	0.293	0.030
	(0.43)	(0.25)	(0.039)	(1.83)	(0.64)	(1.07)	(0.64)	(0.67)	
VAL072	6.92	1.55	0.259	5.54	37.1	41.9	-0.06	0.576	0.042
	(0.53)	(0.19)	(0.024)	(1.04)	(1.23)	(1.09)	(0.37)	(0.44)	
3	—								
4	5.68	1.85	0.218	3.97	34.8	45.0	0.463	0.916	0.0667
	(0.53)	(0.21)	(0.015)	(0.79)	(1.07)	(1.43)	(0.61)	(0.69)	
VAL081	5.64	1.01	0.254	7.53	37.6	40.4	0.372	0.687	0.043
2	(0.20)	(0.13)	(0.024)	(1.11)	(1.12)	(0.57)	(0.68)	(0.71)	
4	—								
5	—								
VAL101	9.16	2.36	0.550	21.6	37.0	39.7	0.189	0.911	0.0322
	(0.43)	(0.08)	(0.130)	(6.07)	(0.50)	(0.61)	(0.29)	(0.37)	
VAL102	7.85	2.16	0.425	15.3	38.6	39.1	0.821	1.08	0.0525
	(0.43)	(0.24)	(0.11)	(4.97)	(0.48)	(0.64)	(0.79)	(0.81)	
3	—								
4	7.68	2.39	0.602	21.2	36.8	39.4	-0.104	0.758	0.186
	(1.67)	(0.63)	(0.95)	(37.8)	(1.02)	(2.98)	(0.33)	(0.43)	
VAL111	5.74	2.76	0.306	9.46	39.9	45.7	0.152	0.363	0.0959
	(0.42)	(0.33)	(0.06)	(3.85)	(0.49)	(0.96)	(0.83)	(0.83)	
2	5.48	1.95	0.226	6.57	38.9	46.0	-0.675	-0.04	0.0881
	(0.84)	(0.31)	0.06	(3.77)	(0.7)	(2.41)	(0.25)	(0.31)	
3	7.16	2.02	0.230	6.16	39.7	42.5	-0.435	0.504	0.039
	(0.81)	(0.16)	(0.03)	(1.58)	(0.75)	(1.51)	(0.21)	(0.28)	
4	7.58	0.941	0.178	3.05	39.3	43.7	-0.175	0.494	0.0476
	(0.67)	(0.13)	(0.09)	(0.431)	(1.15)	(1.00)	(0.27)	(0.33)	
VAL122	4.23	1.53	0.215	4.65	33.0	41.2	-0.683	-0.444	0.122
	(0.36)	(0.81)	(0.038)	(1.28)	(0.78)	(1.38)	(0.56)	(0.6)	
3	4.13	1.17	0.208	4.31	35.3	42.0	-0.567	0.256	0.070
	(0.50)	(0.14)	(0.047)	(1.61)	(0.58)	(1.63)	(0.22)	(0.29)	
4	—								
5	5.53	1.61	0.268	5.30	38.3	40.3	-0.886	-0.04	0.0624
	(0.46)	(0.12)	(0.053)	(1.98)	(0.45)	(1.14)	(0.11)	(0.2)	

continued .....

A.3 continued .....

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	a	b	$\Sigma e^2_{i/m}$
VAL141	7.41	1.93	0.302	7.07	34.8	43.0	0.05	0.377	0.0718
	(0.34)	(0.20)	(0.03)	(0.99)	(0.82)	(1.03)	(0.75)	(0.75)	
2	6.81	1.75	0.387	11.0	36.0	41.2	-0.269	0.343	0.0397
	(0.45)	(0.21)	(0.091)	(3.30)	(0.64)	(1.03)	(0.44)	(0.55)	
3	5.76	1.88	0.231	4.92	38.0	44.6	-0.444	0.138	0.0786
	(0.59)	(0.23)	(0.04)	(1.46)	(1.13)	(1.99)	(0.48)	(0.46)	
4	5.82	1.96	0.282	5.95	37.1	43.1	-0.171	0.356	0.0704
	(0.47)	(0.24)	(0.04	(1.31)	(0.63)	(1.25)	(0.44)	(0.5)	
VAL224	6.02	2.09	0.312	7.61	37.3	40.9	-0.533	0.306	0.030
	(0.38)	(0.14)	(0.042)	(1.64)	(0.31)	(0.78)	(0.16)	(0.22)	
VAL231	8.20	3.35	0.817	29.2	33.2	37.2	0.524	0.790	0.113
	(0.44)	(0.31)	(0.370)	(15.3)	(0.743)	(0.903)	(0.75)	(0.81)	
2	—								
3	—								
VAL251	—								
2	6.40	1.45	0.226	5.61	40.8	43.0	0.026	0.555	0.0466
	(0.57)	(0.33)	(0.027)	(1.07)	(1.02)	(0.96)	(0.47)	(0.58)	
3	4.75	1.48	0.214	4.95	38.0	45.7	-0.198	0.411	0.0461
	(0.40)	(0.14)	(0.031)	(1.20)	(0.52)	(1.43)	(0.41)	(0.42)	
4	6.15	0.9	0.205	4.40	38.7	43.9	-0.187	-0.331	0.0962
	(0.52)	(0.2)	(0.019)	(0.74)	(1.23)	(1.05)	(1.66)	(1.59)	

APPENDIX B

THE MINPAK PACKAGE

B.1 Overall Package Specifics

The MINPAK package for unconstrained Function Minimisation is overviewed in Section 8 of Chapter 5. This appendix discusses specifics.

The main programme in the package is in modularised form and consists of five subroutines called sequentially. Its structure is illustrated in Figure B.1 where an indication is also given as to how the user-written routines are incorporated into the package. The five main subroutines in MINPAK are as follows :-

(1) CONSOL - The main dialogue routine. It allows the user to input the number of parameters (maximum of nine), starting parameters, value of convergence criterion, etc.

(2) PREPRS - The optional user-written data preprocessing routine discussed in Section 8 of Chapter 5. If used, this should be in the Fortran form illustrated in Figure B.1 .

(3) INIT - This routine carries out system specific initialisation, scales the parameters and calculates an initial function value.

(4) OPTMSE - The main function minimisation routine. This is discussed more fully in Section B.2.

(5) CLRUP - The final termination routine.

Both OPTMSE and INIT use the user written function evaluation routine which should be of the Fortran format given in Figure B.1, i.e. have two arguments PAR and F. The first argument is an array used to pass the vector of current parameters (maximum permissable dimension of nine) and the second a real variable in which the user-written routine should return the function value

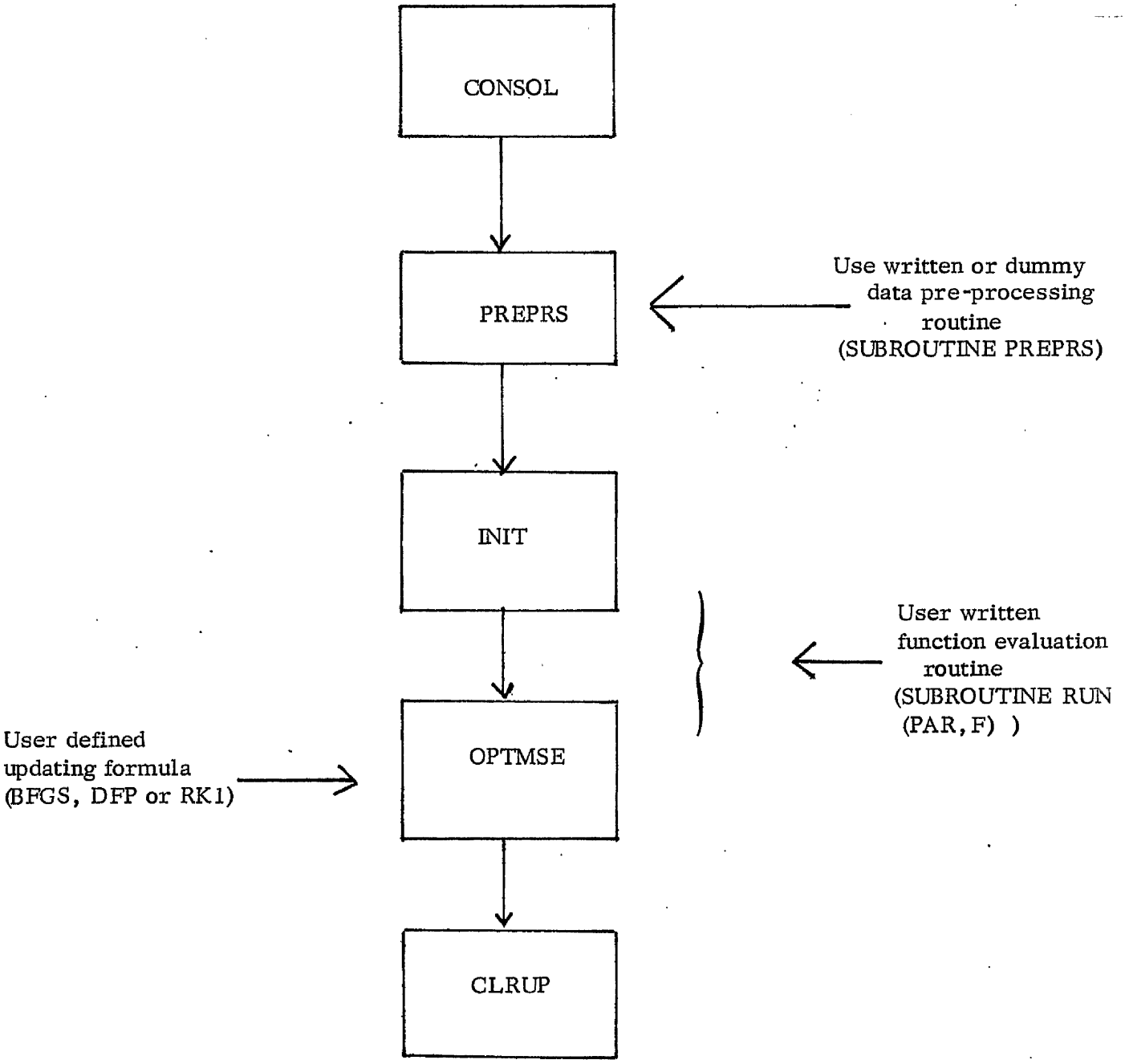


FIGURE B.1 - STRUCTURE OF MINPAK

corresponding to the parameters input. Since parameters are scaled in INIT, it is helpful for the first line of RUN to call the utility routine DSCLE which will descale the parameters for use by the routine, (by carrying out the inverse process to equation 5.38). A skeleton RUN routine thus looks as follows :-

```
      SUBROUTINE RUN (PAR, F )
      DIMENSION PAR (9), PAR1(9)
      CALL DSCLE (PAR, PAR)
      .
     { user written function
     { evaluation code
      .
      .
      RETURN
      END
```

B.2 Main Software Implementation of the Factorised Quasi-Newton Algorithm

This section discusses the subroutine OPTMSE which implements the Factorised Quasi-Newton procedure andthus is the main core of the package. Although OPTMSE differs depending on the choice of updating formula being used (BFGS, DFP, or RK1), the algorithm can be basically represented by the procedure detailed in Table B.1. Various steps in this require elucidation. In the package, gradients are derived numerically. The logic in steps (2), (3), (4), (5) and (8)ensures that a switch is made from forward to the more accurate central differences when difficulty is being encountered with the former. Following Gill et al (125), the interval used for differencing 'h' is $2^{-\frac{t}{2}}$, 't' being the number of binary digits in the mantissa of the machine used (which hence gives 'h' for the PDP11/45 version as 2.4×10^{-4} (single precision version) and 1.5×10^{-8} (double precision version)).

TABLE B.1

FACTORISED QUASI-NEWTON ALGORITHM

(1) Initialise $L^{(0)}$ and $D^{(0)}$ (equation 5.28) for steepest descent step, set I FLAG = ϕ corresponding to gradients calculated by forward differences.

(2) Check that I FLAG = ϕ. If I FLAG does not = ϕ go to step (2).

(3) I FLAG = ϕ, $\therefore$ calculate gradients by forward differences (equation 5.37), use GRAD.

(4) I FLAG = 1 $\therefore$ calculate gradients by central differences (equation 5.38) use GRAD.

(5) Is the norm of the gradient small ? (i.e. $\| g^{(k)} \|_2 < \bar{\gamma}$) if it is and we are only using forward differences return to step (4) to compute a more accurate gradient using central differences.

(6) Solve equation 5.27 to compute direction of search $p^{(k)}$ using first forward then backwards substitution.

(7) Conduct linear search along $p^{(k)}$ using SEARCH which finds the first $\alpha^{(k)}$ along $p^{(k)}$ such that the function value is sufficiently decreased using safeguarded quadratic interpolation (Chapter 5, Section 3).

(8) Is the achieved step small ? (i.e. is $\alpha^{(k)} \| p^{(k)} \|_2 < \bar{\alpha}$). If it is, and we are only using forward differences, abandon this search direction and go back to step (4) to recompute the gradient using a central difference approximation.

(9) Check for convergence to a stationary point (equations B.1 and B.2). If the process has not converged go to step (12).

(10) Carry out local exploratory search to detect if a false minimum has been achieved.

(11) Check if a lower function value $V(\beta)$ has been attained using the local search. If it has not, accept this estimate as the minimum and return to main program. If it has, go to step (14).

(12) Set up scalers π , π_2 , and vectors ω and z (see equations in Chapter 5, Section 5) to update approximate Hessian using either BFGS, DFP or RK1 as appropriate.

(13) Update triangular factors L and D using 'UPDATE' (see Chapter 5, Section 6).

cont'd.....

TABLE B.1 continued .....

(14) Update parameter estimates and gradient vector if FULL PRINT output all the details of current iteration.

(15) Go to step (2).

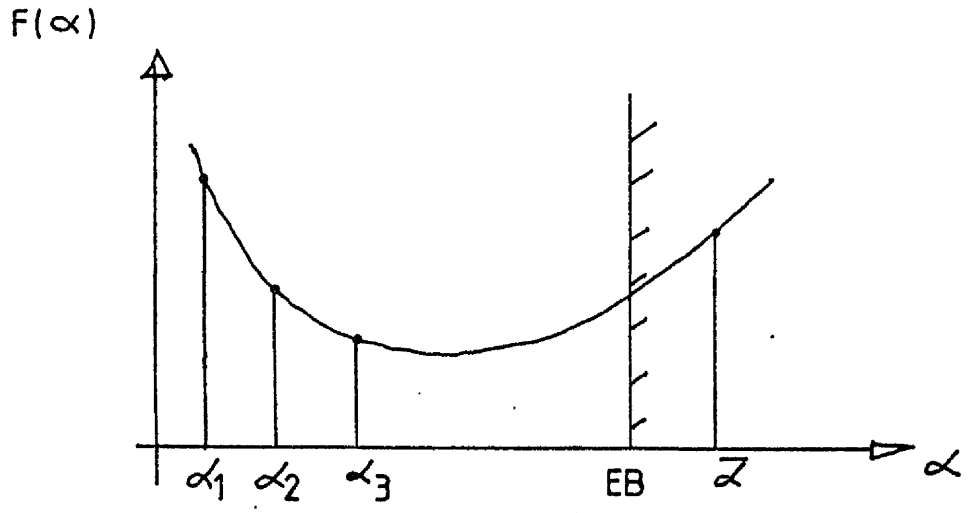


FIG B·2(a)

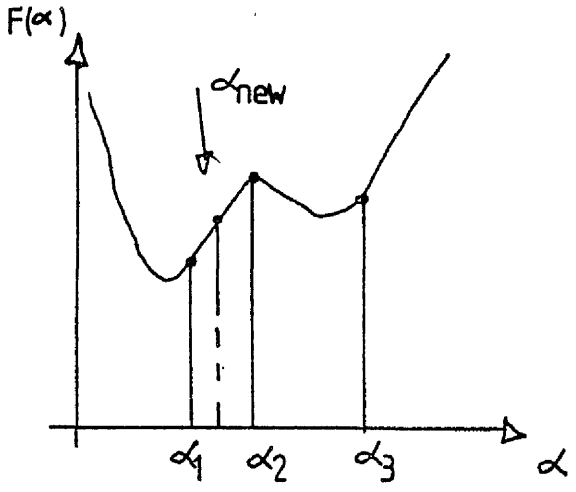


FIG B·2(b)

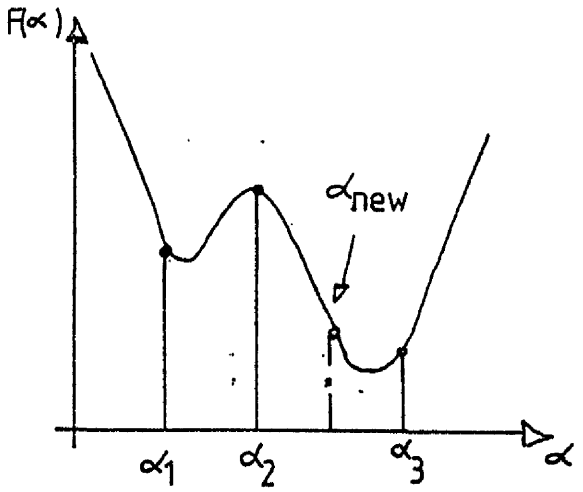


FIG B·2(c)

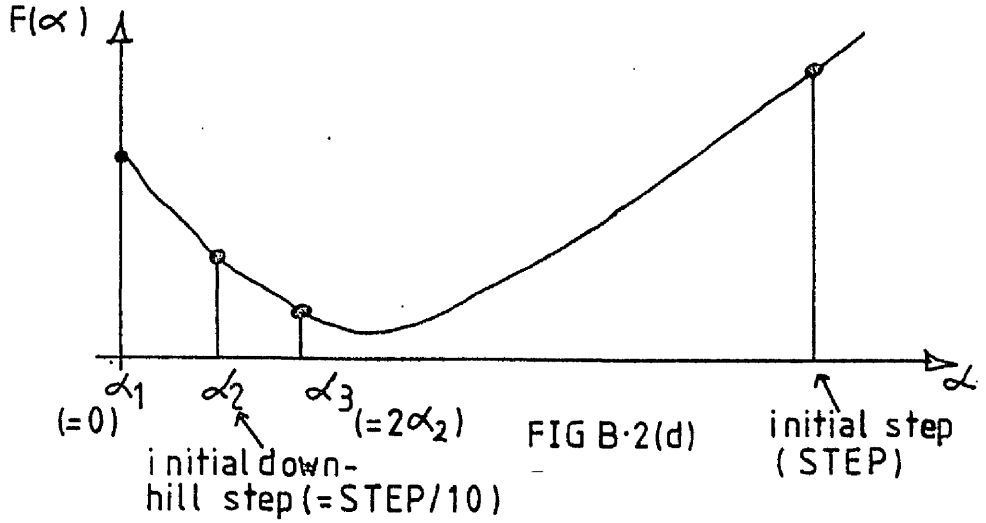


FIG B·2(d)

FIGURE B·2

In step (7) of the algorithm the linear search routine SEARCH is called. This is based on quadratic interpolation, (equation 5.11), but possesses the necessary 'bells and whistles' to render it robust. To safeguard equation 5.11 a predicted step ($\hat{\alpha}$ say) is only accepted if it lies within an extrapolation bound (123) defined e.g. in the case of forwards extrapolation by :

$$EB = 4 (\alpha_3 - \alpha_2) + \alpha_3 \qquad B.1$$

see Figure B.2(a).

SEARCH also makes a limited attempt to handle non-unimodality (see Figures B.2(b) and B.2(c)). In this situation a new point is taken by bisection, according to the following rules :

$$\alpha_{NEW} = (\alpha_1 + \alpha_2) / 2 \quad \text{if} \quad F(\alpha_2) > F(\alpha_3) > F(\alpha_1) \qquad B.2$$

see Figure B.2(b).

$$\alpha_{NEW} = (\alpha_2 + \alpha_3)/2 \quad \text{otherwise} \qquad B.3$$

see Figure B.2(c).

The procedure to generate the initial interpolating points is illustrated in Figure B.2(d). An initial steplength STEP is input by the user in routine CONSOL (usually in the range $0.1 < STEP < 2.0$). If this initial step fails to reduce the function value along the search direction, it is successively reduced by a factor of ten until a downhill step is achieved. The third interpolating point is then twice this initial downhill step. The convergence criterion for the linear search is equation 5.10 in addition to the equation below (which is analagous to equation 5.9 in the situation where analytic gradients are not used).

$$\left| \frac{V(\beta^{(k)} + \hat{\alpha} p^{(k)} - V(\beta^{(k)} + \alpha^{(k)} p^{(k)})}{(V(\beta^{(k)}) - V(\beta^{(k)} + \alpha^{(k)} p^{(k)})} \right| < \eta \qquad B.4$$

A local minimum along the current search direction $p^{(k)}$ is said to have been located when

$$(\alpha_3 - \alpha_1) \; || \; p^{(k)} || \; < \; 0.1 \times 2^{-\frac{t}{2}} \qquad \text{B.5}$$

In step (9) of the algorithm we check for convergence, the criteria used are :

$$|| \beta^{(k+1)} - \beta^{(k)} || \; \leqslant \; 2^{-\frac{t}{2}} \; || \beta^{(k+1)} ||_+ \text{THRES} \qquad \text{B.6}$$

and $$|| g^{(k+1)} || \; \leqslant \; (\text{THRES})^{\frac{1}{3}} \qquad \text{B.7}$$

THRES is a convergence factor input by the user in CONSOL and is usually of the order of 10^{-6} .

Following apparent termination of the basic iteration causes a local search procedure (due to Rosenbrock (249)) to be activated in step (11). The purpose of this is to confirm the solution found by the Quasi- Newton procedure and provide an alternative course of action if, for some reason, a non-stationary point has been located.

B.3 MINPAK Performance in Minimising an Analytic Test Function

This section details the procedure involved in actually using the MINPAK package - in this case to minimise an analytic test function. The particular function used forms a nasty banana shaped valley in two dimensions and is known as Rosenbrock's Parabolic Valley (249). The equation defining this is

$$V(\beta) = 100 (\beta_2 - \beta_1^{\,2})^2 + (1 - \beta_1)^2 \qquad \text{B.8}$$

The minimum of this function is at the point $[\, 1, \;\; 1 \,]$. Starting off at $[\, -1.2, \; 0 \,]$ forces the minimisation method used to negotiate the curve in the valley, a particularly stiff test of Quasi-Newton algorithms since new

search directions must be generated frequently.

A double precision Fortran subroutine coding of equation B.8 is given below :

```
C
C***  FILE : RUND002.FTN  CRAB : 03-FEB-78
C
C***  TEST PROGRAMME NO.2 FOR OPTIMISATION PACKAGE.
C***  DOUBLE PRECISION VERSION.
C
      SUBROUTINE RUN(PAR,F)
      IMPLICIT REAL*8 (A-H,O-Z)
      DIMENSION PAR1(9),PAR(9)
      COMMON ITER
C
C***  UPDATE ITERATION COUNT.
C
      ITER=ITER+1
C
C***  DESCALE THE PARAMETERS.
C
      CALL DSCLE(PAR,PAR1)
C
C***  EVALUATE FUNCTION.
C
      R1=PAR1(1)*PAR1(1)-PAR1(2)
      R2=(1.D0-PAR1(1))*(1.D0-PAR1(1))
      F=100.D0*R1*R1+R2
C
      RETURN
      END
```

After compilation of the above routine using the PDP-11 Fortran compiler, a load programme is then created by invoking the indirect command file for the double precision version of the package, MIND. This initiates the following dialogue (system prompts underlined).

```
 @MIND
>* LOAD PROGRAMME NAME ? [S]: ROSMIN
>* MINIMISATION METHOD (BFGS,DFP,RK1) ? [S]: BFGS
>* PRE-PROCESSING ROUTINE (IF NONE DUMPRSD) ? [S]: DUMPRSD
>* FUNCTION EVALUATION ROUTINE ? [S]: RUND002
```

Having completed the above interaction with the user the indirect command file goes on to create a runnable user programme, called in this case ROSMIN. A sample run of ROSMIN is shown below (system prompts again underlined).

```
MINIMISATION PACKAGE VERSION 2
------------------------------

OPTIMISATION OF (80 CHARS)
? ROSENBROCK'S(1960) PARABOLIC VALLEY.
NOPAR (I1) ?  2
INIT PAR(1) ?  -1.2
INIT PAR(2) ?  1.0
NEED TO SCALE PARS <Y OR N> ?  N
THRES ?  0.1E-05
CONVERGENCE FACTOR FOR LINEAR SEARCH ?  0.1
INITIAL STEP FOR LINEAR SEARCH ?  1.0
FULL PRINT <Y OR N> ?  N
```

The output listing produced from this run is shown in Table B.2. From this it is seen the algorithm successfully reaches the minimum to the desired accuracy in 177 function evaluations. The local search procedure takes 9 function evaluations at the end to confirm the solution. The ' **BFGS' identifier denotes that the BFGS update has been used throughout (the identifier '***LOC' is used if a local search is used at any intermediate stage of the algorithm.)

A more comprehensive assessment of the package performance on this function using different updating algorithms, initial step lengths, STEP, and linear search termination criteria, SIGMA (η) in equation B.4) is detailed in Table B.3. Although the final number of function evaluations (N_F) and final number of iterations (N_{IT}) to achieve the minimum to the desired accuracy (THRES = 10^{-6}) is given, the number of function evaluations required to reduce $V(\beta)$ below 10^{-10} is used as a fairer bench mark for the different algorithms. From Table B.3 it can be seen overall MINPAK performance

compares favourably with the results of Gill et al's coding (125) and Stewart's algorithm (267).

The results also confirm a number of unsubstantiated points made in Chapter 5 regarding e.g. the inadvisability of high accuracy linear search in Quasi-Newton algorithms, the sensitivity of certain updating formulae (e.g. DFP) to the value of linear search termination criterion SIGMA used etc.

TABLE B.2 - LISTING FROM PROGRAMME ROSMIN

```
 MINIMISATION PACKAGE VERSION 2
 ------------------------------

PROBLEM : ROSENBROCK'S (1960) PARABOLIC VALLEY.

NO OF PARAMETERS = 2.

THRESHOLD =  0.10000D-05

CONVERGENCE FACTOR FOR LINEAR  SEARCH =  0.10000D+00

INITIAL STEP FOR LINEAR SEARCH =  0.10000D+01

            PAR(1)       PAR(2)       F(ERR)       NO ITER

SCLNG:

MAXPAR     1.00000      1.00000
MINPAR    0.000000     0.000000


***INI       -1.200        1.000        24.20        1.000
**BFGS       -1.033        1.068        4.135        9.000
**BFGS      -0.9563       0.8835        3.923        14.00
**BFGS      -0.8478       0.6670        3.683        19.00
**BFGS      -0.5706       0.2546        2.970        24.00
**BFGS      -0.5686       0.3237        2.460        30.00
**BFGS      -0.3860       0.1153        2.034        36.00
**BFGS      -0.2791    0.3042E-01       1.862        41.00
**BFGS       0.1700   -0.2588E-02      0.7881        51.00
**BFGS       0.1550    0.1937E-01      0.7162        57.00
**BFGS       0.3080    0.7279E-01      0.5276        66.00
**BFGS       0.4276        0.1528      0.4176        72.00
**BFGS       0.4851        0.2471      0.2791        77.00
**BFGS       0.5818        0.3292      0.1836        83.00
**BFGS       0.6285        0.3776      0.1686        90.00
**BFGS       0.8092        0.6396   0.5956E-01       96.00
**BFGS       0.8006        0.6398   0.3990E-01       103.0
**BFGS       0.8891        0.7837   0.1698E-01       110.0
**BFGS       0.9802        0.9593   0.6177E-03       116.0
**BFGS       0.9788        0.9577   0.4573E-03       122.0
**BFGS       0.9993        0.9983   0.1333E-04       129.0
**BFGS       0.9993        0.9985   0.5408E-06       134.0
**BFGS        1.000         1.000   0.2136E-10       139.0
**BFGS        1.000         1.000   0.1047E-10       147.0
**BFGS        1.000         1.000   0.2138E-11       154.0
**BFGS        1.000         1.000   0.2794E-20       161.0
**BFGS        1.000         1.000   0.2060E-26       168.0

OPTIMUM PARAMETERS :-

            1.000         1.000      0.2060E-26
NUMBER OF ITERATIONS = 177
```

TABLE B.3 : 'MINPAK' PERFORMANCE ON ROSENBROCK'S FUNCTION

STEP	SIGMA	N_F ($V(\beta) < 10^{-10}$)			N_F (FINAL)			N_{IT} (FINAL)		
		BFGS	RK1	DFP	BFGS	RK1	DFP	BFGS	RK1	DFP
0.1	0.0	406	509	451	416	546	461	22	26	22
0.1	0.1	182	227	232	200	236	250	26	34	32
0.1	0.3	184	205	161	200	213	175	28	31	29
0.1	1.0	206	278	520	247	299	559	40	56	55
1.0	0.0	504	417	351	536	458	359	23	26	22
1.0	0.1	139	183	214	168	190	228	26	30	33
1.0	0.3	157	159	245	164	173	261	29	28	35
1.0	1.0	150	170	265	164	184	305	30	33	36
2.0	0.0	354	238	419	392	264	429	23	26	22
2.0	0.1	156	160	293	165	184	310	25	27	45
2.0	0.3	157	140	139	174	148	168	28	24	27
2.0	1.0	152	172	281	160	179	296	28	31	55

BEST

MINPAK	139	140	139
Gill and Murray Implementation	126	150	148
Stewart		174	

APPENDIX C

THE NLSPAK PACKAGE

C.1 Overall Package Specifics

Like the MINPAK package described in the previous Appendix, NLSPAK is Fortran-based and runs under the DEC RSX-11M and RT-11 operating systems. However, due to memory limitations on the PDP-11/45, NLSPAK, unlike MINPAK, is only available in single precision. The package caters for data lengths of up to 250 points. Due to its size, MINPAK is heavily overlaid (Overlaying is a facility on the PDP-11 allowing segmentation of a load program so that the whole program need not be simultaneously memory-resident, thus allowing execution of a program which otherwise would not fit into the available memory). This overlay structure is effectively transparent to the user at run-time, but it increases programme execution time. This time increase is minimised in NLSPAK by judicious arrangement of the over-lay segments.

The large size of the NLSPAK load programme is not primarily due to the large number of instructions in the package, but rather to the large amount of array storage which is required (9K words for the sensitivity matrix X, the vector of residuals e and the perturbed values required when calculating 2nd. derivative finite difference information. This is large in proportion to the total memory available to the programme (23K - RT - 11, 32K - RSX-11M)).

Although overlaying makes the resultant link procedure for the package relatively complicated, as in the case for MINPAK, this is made inivisible to the user by using an indirect command file to carry this out interactively. The outline structure of the package is basically the same as

for MINPAK (see Figure B.1). However, there is no choice of minimisation algorithm in this case.

Also, the user's function evaluation routine 'RUN' must supply 1st derivative information in the form of the sensitivity matrix X . This routine should, therefore, have the following format.

```
      SUBROUTINE RUN (PAR, E, X, F, M, N )
      DIMENSION PAR(N), E(M), X(M,N), F(M).
      .
      .
      { user-written code to return residuals E,
      { sensitivity matrix X and sum of squared
      { errors F as a function of the parameters PAR.
      .
      .
      RETURN
      END
```

It can be seen that writing a 'RUN' routine for NLSPAK involves considerably more programming effort on the part of the user than writing the corresponding routine for MINPAK. NLSPAK is therefore less attractive in this sense. However, use can be made of this cheap residual and sensitivity information in data-fitting applications to assess adequacy of fit. In NLSPAK, the 'CLRUP' routine is used to compute diagnostic information derived from X and e. It optionally computes the mean and variance of the residuals, the covariance matrix of the parameters, the parameter correlation matrix, the 95% confidence limits for each estimated parameter and the volume of the 95% confidence ellipsoid in parameter space (see Chapter 4 for discussion of these quantities). It also gives a graphical output (print-plot) of the vector of residuals and its auto-correlation function on the line printer.

TABLE C.1

NON-LINEAR LEAST SQUARES ALGORITHM

(1) Set up flags, initial variables and set initial grade of the sensitivity matrix X ' r ' = 'n' the number of parameters.

(2) Use 'RUN' to get initial m x n sensitivity matrix X, vector of errors e and sum of squares $V(\beta)$.

(3) Calculate initial gradient vector $g^{(0)}$ (i.e. using equation 6.2 $g = 2X^T e$).

(4) Compute singular value decomposition of sensitivity matrix $X = U S V^T$ (see equation 6.10) using 'SVD'.

(5) If this is the first iteration of the algorithm go to step (9) to take full Gauss-Newton step.

(6) Fix the grade 'r' of X based on the relative function decrement achieved in the previous iteration using 'IGRADE'.

(7) Compute $e^* = U^T e$

(8) If the grade 'r' is zero go to step (11) (i.e. there is no $p_{(1)}$ component here in equation 6.20).

(9) Compute Gauss-Newton direction in space spanned by the column by column partition of V corresponding to the grade 'r' calculated in (6), i.e. use $p_{(1)} = -V_1 S_1^{-1} e_1$ (this is equivalent to equation 6.17 with $e_1^* = U_1^T e$.)

(10) If grade 'r' = 'n' the number of parameters go to step (15),(i.e. there is no $p_{(2)}$ component here in equation 6.20).

(11) Approximate second derivative dependent matrix $Y = V_2^T B^{(k)}$ by finite differences as described in section 6.3, use routine 'HESS'.

(12) Form strict lower triangle of $A = (S_2^2 + Y V_2)$ (see equation 6.18) and pack row by row in a linear array for use by the modified Cholisky Factorisation algorithm. Form vector $b = -S_2 e_2^* - Yp_{(1)}$ corresponding to the right-hand side of equation 6.18.

Table C.1 continued .....

(13) Use the modified Cholesky factorisation algorithm (routine 'MDCHOL') to compute Cholesky factors of A above.

(14) Solve resultant linear equation set $A\,y = b$ where the Cholesky factors of A have been computed in (13) above, by first forward and then backwards substitution. Use routine 'LINSOL'. Computer $p_{(2)} = V_2\,y$ (see equation 6.19).

(15) Compute resultant search direction $p^{(k)} = p_{(1)} + p_{(2)}$ (equation 6.20).

(16) Compute $\|p^{(k)}\|$, $\|g^{(k)}\|$ and $\|g^{(k)T}\,p^{(k)}\|$ if $\frac{-g^t\,p}{\|g\|\,\|p\|} < \xi$ where ξ is a small scalar. Set grade 'r' = 'n' the number of parameters.

(17) Output current parameters, gradients sums of squares, etc.

(18) Conduct linear search to find a suitable steplength $\alpha^{(k)}$ which sufficiently reduces $V(\beta)$ along $p^{(k)}$. Use routine SEARCH (also uses INTERP, EVAL, SCNVGD).

(19) Check for convergence of algorithm (use routine CNVGD).

(20) If convergence criteria in (19) are not satisfied update parameters and gradient and go to step (4).

(21) Return.

C.2 Main Software Implementation of the Non-Linear Least Squares Algorithm

The main core of the NLSPAK package is the implementation of Gill and Murray's Non-Linear Least Squares algorithm (124) which is contained in the subroutine 'OPTMSE'. The calculation steps constituting 'OPTMSE' are detailed in Table C.1. Some of these steps will be further explained below.

Step (16) of the algorithm is a check to ensure that the approximation to the Hessian matrix obtained is not indefinite. The search direction must be recomputed with grade 'r' equal to zero if this is suspected. This is because the modified Cholesky Factorisation (123a) must be calculated in the space spanned by all the columns of V to allow it to shift all the negative eigenvalues of $X^T X + B$ (see equation 6.6) to maintain positive-definiteness.

In step (18) the linear search problem is solved using a safeguarded cubic interpolation algorithm (since gradient information is assumed available here). Only two points are needed for interpolation in this case (see Section 3 in Chapter 5) and formulae 5.12, 5.13, and 5.14 are used to compute the stationary point. For extrapolation purposes these formulae can be safeguarded by placing bounds on the predicted steplength in a manner similar to that discussed for quadratic extrapolation in Appendix B. Equations 5.9 and 5.10 are used as a basis for termination of the linear search. Good choices of the linear search termination criterion η and the initial steplength in this algorithm are 0.9 and 1.0 respectively (124). This choice implies that a single step along the search direction $p^{(k)}$ is nearly always accepted provided the sum of squares $V(\beta)$ is sufficiently reduced.

The criteria used in step (19) to check for final convergence of the algorithm are as follows :-

$$\alpha^{(k)} \; \|p^{(k)}\| \leq (\text{THRES})\,(1 + \|\beta^{(k)}\|) \qquad \text{C.1}$$

and

$$\left| \frac{V(\beta^{(k)}) - V(\beta^{(k-1)})}{(1 + V(\beta^{(k)})} \right| \leq \text{THRES}^2 \qquad \text{C.2}$$

$$\|g^{(k)}\| \leq 2^{-\frac{t}{3}} \; (1 + V(\beta^{(k)})) \qquad \text{C.3}$$

or

and

$$\|g^{(k)}\| < V(\beta^{(k)})^{\frac{1}{2}} \; 2^{\frac{-t}{2}} \qquad \text{C.4}$$

or

$$V(\beta^{(k)}) < 2^{-2t} \qquad \text{C.5}$$

As in Appendix B, THRES is the convergence factor input by the user in 'CONSOL' and 't' is the length of the binary mantissa of the computer used (t = 24 is appropriate for single precision computation on the PDP 11/45).

C.3 NLSPAK Performance on Minimising an Analytic Test Function

We will now illustrate the use of NLSPAK by minimising the same analytic test function (Rosenbrock's parabolic valley (249)) as was used to test the Factorised Quasi-Newton Minimisation algorithm in Appendix B.

The test function (defined by equation B.8), can be interpreted as a sum of squares (m = 2, n = 2) by defining e as

$$e(\beta)^T = \left[10\,(\beta_2 - \beta_1)^2 \qquad (1 - \beta_1) \right] \qquad \text{C.6}$$

The sensitivity matrix X is readily calculated as :-

$$X(\beta) = \begin{bmatrix} -20\beta_1 & 10 \\ -1 & 0 \end{bmatrix} \qquad \text{C.7}$$

The 'RUN' subroutine for this function is shown below.

```
C
C***  FILE : ROSRUN.FTN  (RAB : 26-JAN-78)
C
C***  LEAST SQUARES VERSION OF ROSENBROCK'S TEST FN.
C
      SUBROUTINE RUN(PAR,F,RJ,FX,IU,IV)
      DIMENSION PAR(6),F(IU),RJ(IU,IV)
      COMMON ITER,NOPAR,NPTS
C
      NPTS=2
      ITER=ITER+1
      F(1)=10.0*(PAR(2)-PAR(1)*PAR(1))
      F(2)=1.0-PAR(1)
      FX=F(1)*F(1)+F(2)*F(2)
      RJ(1,1)=-20.0*PAR(1)
      RJ(1,2)=10.0
      RJ(2,1)=-1.0
      RJ(2,2)=0.0
      RETURN
      END
```

Once compiled this routine can be linked into the package using an indirect command file in a similar way to that described for MINPAK in Appendix B.

The results obtained using NLSPAK on Rosenbrock's function for differing initial steplengths (STEP) and linear search termination criteria (SIGMA) are summarised in Table C.2. From this it is seen the best performance is achieved with the values of the linear search parameters set to those recommended in the previous section of this Appendix.

To compare the results in Table C.2 on a fair basis with those obtained using the Factorised Quasi-Newton algorithm we define an index of computational labour (300) for the non-linear least squares algorithm as

$$n_c = n_f + n\ n_g \qquad \text{C.8}$$

where 'n_f' is the number of function evaluations, 'n' the number of parameters

and ' n_g ' the number of gradient evaluations. Thus for this problem it is seen that one call to 'RUN' using the non-linear least squares algorithm is equivalent to three using the Factorised Quasi-Newton algorithm.

Comparing the two sets of results in this manner (again see Table C.2) it is evident tha the non-linear least squares algorithm is markedly superior to the Factorised Quasi-Newton algorithm on this particular problem (despite the disadvantages of being implemented only in single precision).

STEP	SIGMA	$N_{F,G}(V(\beta)<10^{-10}$		N_{IT}	N_F (Final)
		$N_{f,g}$	N_c		
0.1	0.0	918	2754	20	936
0.1	0.1	34	102	18	51
0.1	0.3	34	102	18	52
0.1	0.9	110	330	110	140
1.0	0.0	945	2835	19	946
1.0	0.1	44	132	15	45
1.0	0.3	36	108	14	37
1.0	0.9	33	99	13	35
2.0	0.0	854	2562	25	855
2.0	0.1	55	165	16	56
2.0	0.5	45	135	15	51
2.0	0.9	44	132	15	45

BEST

(Least Squares (N_c)	99
Factorised Quasi Newton	139

TABLE C.2 : NON-LINEAR LEAST SQUARES PACKAGE PERFORMANCE ON ROSENBROCK'S FUNCTION

APPENDIX D

COUPLING TERMS AND INITIAL CONDITIONS FOR THE CO_2 GAS TRANSPORT MODEL SENSITIVITY EQUATIONS

(A). Four Parameter Model

(i) Coupling Terms

$$C_1(\dot{Q}) = \left[b(P_{TC} - P_A) + A_{INT} \right] \text{ const} \qquad D.1$$

$$C_2(\dot{Q}) = -b(P_{TC} - P_A) - A_{INT} \qquad D.2$$

$$C_1(V_A) = -\frac{\dot{V}}{V_A^2}(P_I^* - P_A) - \frac{\dot{Q}}{V_A^2}\left[b(P_{TC} - P_A) + A_{INT} \right] \text{ const.} \qquad D.3$$

$$C_2(V_A) = 0 \qquad D.4$$

$$C_1(\dot{M}) = 0 \qquad D.5$$

$$C_2(\dot{M}) = 1 \qquad D.6$$

$$C_1(V_{TC}) = 0 \qquad D.7$$

$$C_2(V_{TC}) = -\frac{\dot{M}}{bV_{TC}^2} + \frac{\dot{Q}}{bV_{TC}^2}\left[b(P_{TC} - P_A) + A_{INT} \right] \qquad D.8$$

(ii) Initial Conditions

$$P_{A(0)} = \text{assumed value (see Chapter 3)} \qquad D.9$$

$$P_{TC(0)} = P_{ABAR} + \frac{\dot{M}}{b\dot{Q}} - \frac{A_{INT}}{b} \text{ (see equation 3.14)} \qquad D.10$$

$$\frac{\partial P_{A(0)}}{\partial \dot{Q}} = 0 \qquad D.11$$

$$\frac{\partial P_{TC(0)}}{\partial \dot{Q}} = -\frac{\dot{M}}{b\dot{Q}^2} \qquad D.12$$

$$\frac{\partial P_{A(0)}}{\partial V_A} = 0 \qquad D.13$$

$$\frac{\partial P_{TC(0)}}{\partial V_A} = 0 \qquad D.14$$

$$\frac{\partial P_{A(0)}}{\partial \dot{M}} = 0 \qquad \text{D.15}$$

$$\frac{\partial P_{TC(0)}}{\partial \dot{M}} = \frac{1}{b\bar{Q}} \qquad \text{D.16}$$

$$\frac{\partial P_{A(0)}}{\partial V_{TC}} = 0 \qquad \text{D.17}$$

$$\frac{\partial P_{TC}}{\partial V_{TC}} = 0 \qquad \text{D.18}$$

(B). Five Parameter Model

(i) Coupling Terms

Additional coupling terms extra to those detailed above are :-

$$C_1 (P_{A(0)}) = 0 \qquad \text{D.19}$$

$$C_2 (P_{A(0)}) = 0 \qquad \text{D.20}$$

(ii) Initial Conditions

Initial conditions for all the parameters are the same as for the four parameter case, except for the following :-

$$P_{A(0)} = P_{A(0)} \qquad \text{D.21}$$

$$\frac{\partial P_{A(0)}}{\partial P_{A(0)}} = 1 \qquad \text{D.22}$$

$$\frac{\partial P_{TC(0)}}{\partial P_{A(0)}} = 1 \qquad \text{D.23}$$

(C). Six Parameter Model

(i) Coupling Terms

Additional coupling terms extra to those detailed above are :-

$$C_1 (P_{TC(0)}) = 0 \qquad \text{D.24}$$

$$C_2 (P_{TC(0)}) = 0 \qquad \text{D.25}$$

(ii) Initial Conditions

Initial conditions for all the model parameters are the same as for the five parameter case, except for the following :-

$$P_{TC(0)} = P_{TC(0)} \qquad \text{D.26}$$

$$\frac{\partial P_{TC(0)}}{\partial \dot{Q}} = 0 \qquad \text{D.27}$$

$$\frac{\partial P_{TC(0)}}{\partial \dot{M}} = 0 \qquad \text{D.28}$$

$$\frac{\partial P_{TC(0)}}{\partial P_{A(0)}} = 0 \qquad \text{D.29}$$

$$\frac{\partial P_{A(0)}}{\partial P_{TC(0)}} = 0 \qquad \text{D.30}$$

$$\frac{\partial P_{TC(0)}}{\partial P_{TC(0)}} = 1 \qquad \text{D.31}$$

APPENDIX E

E.1 : REPRODUCIBILITY DATA : ESTIMATION RESULTS - SIX PARAMETERS.

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	$\Sigma e_i^2 / m$
REP011	7.11 ± 0.18	2.59 ± 0.11	0.257 ± 0.0016	3.37 ± 0.13	43.5 ± 0.68	44.5 ± 0.43	0.283
3	6.46 ± 0.14	2.81 ± 0.10	0.277 ± 0.0027	3.34 ± 0.13	37.5 ± 0.82	44.3 ± 0.48	0.252
4	6.81 ± 0.14	2.69 ± 0.09	0.291 ± 0.0026	3.29 ± 0.10	36.4 ± 0.68	44.0 ± 0.42	0.249
REP021	5.35 ± 0.15	3.36 ± 0.15	0.251 ± 0.0007	4.32 ± 0.28	38.8 ± 0.75	47.0 ± 0.5	0.230
2	6.33 ± 0.21	2.67 ± 0.13	0.230 ± 0.0007	2.66 ± 0.08	43.0 ± 0.58	42.0 ± 0.48	0.300
4	7.93 ± 0.23	1.34 ± 0.11	0.222 ± 0.0009	3.16 ± 0.07	50.0 ± 0.88	40.8 ± 0.44	0.341
5	5.29 ± 0.20	2.54 ± 0.17	0.241 ± 0.0009	3.12 ± 0.14	35.8 ± 0.76	44.4 ± 0.62	0.372
REP071	6.46 ± 0.29	3.05 ± 0.23	0.240 ± 0.0009	3.98 ± 0.23	39.3 ± 1.03	43.5 ± 0.67	0.301
2	4.78 ± 0.16	5.67 ± 0.25	0.226 ± 0.0043	24.4 ± 15.6	40.1 ± 0.69	50.7 ± 0.55	0.427
3	6.21 ± 0.29	2.89 ± 0.21	0.236 ± 0.0014	3.85 ± 0.25	48.2 ± 0.96	47.1 ± 0.60	0.342
4	5.70 ± 0.18	3.25 ± 0.19	0.250 ± 0.0016	5.04 ± 0.43	41.1 ± 0.73	49.6 ± 0.46	0.248
REP081	6.42 ± 0.18	3.54 ± 0.14	0.215 ± 0.0014	4.38 ± 0.21	34.6 ± 0.62	41.6 ± 0.35	0.122
2	5.88 ± 0.15	3.46 ± 0.12	0.216 ± 0.0012	4.20 ± 0.17	34.3 ± 0.64	38.7 ± 0.40	0.141
3	5.18 ± 0.18	2.44 ± 0.16	0.205 ± 0.0024	4.10 ± 0.27	36.8 ± 1.0	40.4 ± 0.52	0.232
4	4.79 ± 0.16	2.97 ± 0.16	0.203 ± 0.0025	5.18 ± 0.63	36.3 ± 0.92	41.8 ± 0.53	0.345
REP091	4.96 ± 0.15	4.01 ± 0.12	0.222 ± 0.0015	3.39 ± 0.14	31.8 ± 0.52	38.6 ± 0.58	0.186
2	5.60 ± 0.31	3.08 ± 0.17	0.196 ± 0.0013	2.29 ± 0.09	34.2 ± 0.69	35.2 ± 0.79	0.413
3	4.67 ± 0.19	3.56 ± 0.15	0.205 ± 0.0021	2.61 ± 0.12	31.9 ± 0.69	38.1 ± 0.77	0.242
4	4.01 ± 0.10	4.24 ± 0.12	0.207 ± 0.0021	4.97 ± 0.44	32.7 ± 0.59	39.4 ± 0.61	0.283
REP111	5.69 ± 0.29	2.97 ± 0.25	0.215 ± 0.0036	2.45 ± 0.26	35.2 ± 1.43	38.9 ± 0.64	0.523
2	4.98 ± 0.21	3.48 ± 0.21	0.222 ± 0.0018	3.08 ± 0.14	35.2 ± 1.01	38.1 ± 0.75	0.391
3	5.42 ± 0.27	3.28 ± 0.15	0.191 ± 0.0035	2.32 ± 0.08	35.8 ± 1.18	37.3 ± 0.94	0.543
4	5.05 ± 0.19	3.22 ± 0.17	0.185 ± 0.0019	2.24 ± 0.09	32.4 ± 0.86	35.6 ± 0.92	0.457

cont'd.....

E.1 continued .....

File	$\dot{Q}$	$\dot{V}_A$	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	$\Sigma e_i^2 / m$
REP121	5.80 ± 0.11	3.06 ± 0.17	0.239 ± 0.0025	4.47 ± 0.11	44.4 ± 0.97	47.4 ± 0.67	0.261
2	6.76 ± 0.18	2.77 ± 0.19	0.237 ± 0.0021	2.53 ± 0.16	41.6 ± 0.55	48.3 ± 0.84	0.538
3	7.48 ± 0.18	2.40 ± 0.25	0.213 ± 0.0031	2.76 ± 0.17	48.1 ± 1.25	39.5 ± 0.72	1.02
4	6.38 ± 0.21	3.29 ± 0.16	0.259 ± 0.0030	3.41 ± 0.13	38.1 ± 1.01	46.7 ± 0.61	0.546
REP141	5.48 ± 0.21	2.19 ± 0.22	0.206 ± 0.0009	4.05 ± 0.11	40.4 ± 0.72	44.6 ± 0.45	0.265
2	5.05 ± 0.08	2.38 ± 0.08	0.189 ± 0.0007	3.83 ± 0.13	38.3 ± 0.87	47.4 ± 0.41	0.189
3	5.28 ± 0.15	2.15 ± 0.09	0.196 ± 0.001	3.42 ± 0.18	39.7 ± 0.64	43.7 ± 0.36	0.272
4	5.56 ± 0.13	1.76 ± 0.25	0.205 ± 0.0021	3.95 ± 0.32	39.3 ± 0.89	46.9 ± 0.78	0.201
REP151	7.48 ± 0.20	2.63 ± 0.13	0.217 ± 0.0017	5.01 ± 0.54	38.6 ± 1.05	41.8 ± 0.75	0.294
2	6.28 ± 0.19	3.41 ± 0.13	0.225 ± 0.0012	3.83 ± 0.16	36.9 ± 0.87	44.1 ± 0.53	0.351
3	5.73 ± 0.26	3.77 ± 0.17	0.208 ± 0.0018	4.28 ± 0.20	37.4 ± 0.92	42.9 ± 0.82	0.188
4	5.59 ± 0.17	3.34 ± 0.17	0.208 ± 0.0014	4.15 ± 0.17	39.0 ± 0.63	42.7 ± 0.56	0.269
REP181	6.37 ± 0.19	3.98 ± 0.08	0.253 ± 0.0021	2.49 ± 0.19	34.9 ± 0.82	39.9 ± 0.71	0.236
2	6.70 ± 0.25	3.29 ± 0.19	0.281 ± 0.0022	2.59 ± 0.09	35.9 ± 0.65	36.6 ± 0.52	0.243
3	5.83 ± 0.17	3.73 ± 0.12	0.286 ± 0.0030	2.86 ± 0.08	34.8 ± 0.76	38.1 ± 0.66	0.305
4	5.69 ± 0.28	3.78 ± 0.17	0.266 ± 0.0029	2.47 ± 0.42	35.5 ± 0.49	39.5 ± 0.84	0.277
REP191	6.84 ± 0.26	3.69 ± 0.19	0.277 ± 0.0022	3.50 ± 0.11	36.4 ± 0.67	41.8 ± 0.56	0.172
2	6.72 ± 0.26	3.46 ± 0.21	0.264 ± 0.0031	2.79 ± 0.19	37.6 ± 0.79	39.5 ± 0.75	0.254
3	5.23 ± 0.24	4.27 ± 0.16	0.284 ± 0.0030	3.85 ± 0.16	34.7 ± 0.91	40.6 ± 0.79	0.314
4	4.83 ± 0.21	5.70 ± 0.14	0.285 ± 0.0026	4.88 ± 0.22	34.9 ± 0.42	44.6 ± 0.84	0.316
REP201	5.38 ± 0.09	2.87 ± 0.17	0.185 ± 0.0016	4.85 ± 0.18	36.9 ± 0.75	43.2 ± 0.25	0.176
2	4.88 ± 0.19	2.51 ± 0.19	0.172 ± 0.0018	3.94 ± 0.19	38.5 ± 0.64	43.4 ± 1.06	0.193
3	5.10 ± 0.21	2.80 ± 0.09	0.179 ± 0.0022	4.63 ± 0.21	38.7 ± 0.83	43.4 ± 0.52	0.104
4	5.43 ± 0.13	2.27 ± 0.10	0.176 ± 0.0014	3.60 ± 0.12	38.8 ± 0.58	41.3 ± 0.35	0.145

E2 : REPRODUCIBILITY DATA

Estimation Results - Eight Parameters

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	a	b	$\sum e^2_{i/m}$
REP011	7.11	2.92	0.276	3.86	3.89	45.1	0.95	0.36	0.131
	(0.2)	(0.091)	(0.0075)	(0.28)	(0.61)	(0.86)	(0.054)	(0.10)	
3	6.83	2.76	0.275	3.32	38.2	43.5	-0.68	-0.10	0.164
	(0.21)	(0.11)	(0.003)	(0.2)	(0.75)	(0.69)	(0.11)	(0.14)	
4	7.07	2.84	0.288	3.46	37.4	43.1	-0.81	-0.25	0.150
	(0.22)	(0.10)	(0.0034)	(0.24)	(0.6)	(0.71)	(0.09)	(0.17)	
REP021	5.74	3.18	0.251	3.92	38.2	46.1	-0.93	-0.32	0.069
	(0.21)	(0.10)	(0.0028)	(0.34)	(0.45)	(0.75)	(0.05)	(0.09)	
2	6.15	2.76	0.234	2.91	37.6	44.8	-0.96	-0.51	0.142
	(0.29)	(0.13)	(0.0043)	(0.23)	(0.61)	(0.96)	(0.05)	(0.09)	
4	6.49	2.70	0.229	3.86	38.5	43.9	-0.98	-0.32	0.095
	(0.27)	(0.17)	(0.010)	(0.36)	(0.54)	(0.89)	(0.03)	(0.09)	
5	6.11	2.46	0.242	2.98	37.1	42.0	-0.94	-0.31	0.103
	(0.31)	(0.12)	(0.004)	(0.25)	(0.54)	(0.96)	(0.04)	(0.09)	
REP071	6.46	3.37	0.241	4.36	37.5	44.3	-0.7	0.08	0.148
	(0.41)	(0.24)	(0.0021)	(0.56)	(0.67)	(0.9)	(0.09)	(0.13)	
2	6.29	3.95	0.229	4.59	40.9	47.6	-0.92	-0.34	0.220
	(0.43)	(0.25)	(0.005)	(0.8)	(0.76)	(1.25)	(0.07)	(0.11)	
3	6.58	3.11	0.241	4.09	44.6	46.8	-0.88	-0.32	0.192
	(0.39)	(0.20)	(0.0036)	(0.53)	(0.98)	(1.06)	(0.08)	(0.12)	
4	5.89	3.39	0.249	5.30	41.7	48.9	-0.79	-0.36	0.176
	(0.27)	(0.21)	(0.0026)	(0.78)	(0.73)	(0.77)	(0.15)	(0.17)	
REP081	6.43	3.62	0.213	4.47	35.4	41.2	-0.546	-0.049	0.093
	(0.23)	(0.14)	(0.0016)	(0.32)	(0.39)	(0.47)	(0.16)	(0.18)	
2	5.97	3.51	0.217	4.22	33.9	38.7	-0.747	-0.418	0.114
	(0.27)	(0.17)	(0.002)	(0.67)	(0.42)	(0.31)	(0.11)	(0.12)	
3	5.25	2.37	0.205	4.11	37.0	40.3	0.135	0.210	0.232
	(0.28)	(0.19)	(0.0022)	(0.94)	(0.65)	(0.72)	(0.11)	(0.21)	
4	4.90	3.03	0.203	5.10	36.0	41.6	-0.588	0.02	0.224
	(0.25)	(0.20)	(0.0029)	(0.95)	(0.87)	(0.80)	(0.11)	(0.14)	
REP091	5.36	3.72	0.221	3.19	32.1	37.4	-0.45	0.19	0.125
	(0.24)	(0.16)	(0.0019)	(0.18)	(0.54)	(0.76)	(0.12)	(0.15)	
2	5.68	3.36	0.199	2.38	32.1	36.4	-0.81	-0.28	0.261
	(0.47)	(0.20)	(0.0027)	(0.24)	(0.78	(1.35)	(0.11)	(0.13)	
3	6.72	2.83	0.202	2.27	33.2	33.7	-0.87	-0.33	0.146
	(0.44)	(0.15)	(0.0034)	(0.16)	(0.78)	(1.03)	(0.08)	(0.12)	
4	5.65	3.17	0.200	2.81	33.9	34.7	-0.90	-0.33	0.176
	(0.36)	(0.16)	(0.0042)	(0.27)	(0.73)	(1.18)	(0.07)	(0.11)	
REP111	5.81	2.99	0.213	2.47	35.9	38.4	-0.67	-0.26	0.410
	(0.37)	(0.19)	(0.0039)	(0.15)	(1.28)	(1.25)	(0.17)	(0.19)	

continued .....

E.2 continued .....

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	a	b	$\Sigma e_{i/m}^2$
REP112	5.22	3.36	0.219	2.99	36.1	37.1	-0.45	0.193	0.263
	(0.22)	(0.14)	(0.003)	(0.18)	(0.88)	(0.95)	(0.12)	(0.15)	
3	5.44	3.43	0.192	2.32	35.0	37.7	-0.66	-0.167	0.384
	(0.36)	(0.18)	(0.0039)	(0.15)	(1.12)	(1.33)	(0.13)	(0.16)	
4	5.38	3.20	0.189	2.23	30.9	36.3	-0.75	-0.07	0.234
	(0.30)	(0.12)	(0.0035)	(0.15)	(0.92)	(1.30)	(0.09)	(0.12)	
REP121	6.56	2.70	0.240	4.10	44.0	46.7	-0.90	-0.47	0.169
	(0.21)	(0.11)	(0.004)	(0.28)	(0.84)	(0.76)	(0.1)	(0.13)	
2	6.76	3.19	0.239	2.60	40.4	48.4	-0.68	0.04	0.314
	(0.43)	(0.17)	(0.003)	(0.20)	(1.03)	(1.25)	(0.1)	(0.13)	
3	6.58	3.44	0.225	3.05	39.7	42.7	-0.91	-0.2	0.337
	(0.43)	(0.16)	(0.0065)	(0.36)	(0.95)	(1.61)	(0.05)	(0.1)	
4	6.89	3.34	0.255	3.56	39.8	44.8	-0.82	-0.11	0.248
	(0.35)	(0.14)	(0.0043)	(0.34)	(0.78)	(1.09)	(0.07)	(0.11)	
REP141	5.72	2.09	0.206	3.90	40.6	44.2	-0.623	-0.03	0.173
	(0.17)	(0.10)	(0.0016)	(0.22)	(1.01)	(0.68)	(0.12)	(0.15)	
2	5.21	2.37	0.190	3.82	38.8	46.8	-0.625	0.06	0.112
	(0.14)	(0.09)	(0.0015)	(0.24)	(0.73)	(0.57)	(0.11)	(0.13)	
3	5.49	2.20	0.197	3.42	39.2	43.6	-0.644	0.03	0.146
	(0.18)	(0.08)	(0.0023)	(0.21)	(0.68)	(0.67)	(0.09)	(0.12)	
4	5.61	1.80	0.205	3.96	39.7	46.7	-0.495	0.13	0.134
	(0.22)	(0.08)	(0.0014)	(0.19)	(0.77)	(0.45)	(0.12)	(0.14)	
REP151	8.26	2.40	0.216	4.70	39.6	40.6	-0.897	-0.998	0.192
	(0.30)	(0.13)	(0.0046)	(0.33)	(1.66)	(0.73)	(0.11)	(0.13)	
2	6.32	3.41	0.224	3.86	37.9	43.6	-0.585	-0.293	0.322
	(0.24)	(0.15)	(0.0018)	(0.23)	(1.03)	(0.73)	(0.24)	(0.25)	
3	6.13	3.60	0.208	4.04	37.5	42.1	-0.815	-0.429	0.142
	(0.18)	(0.10)	(0.0023)	(0.25)	(0.56)	(0.58)	(0.14)	(0.16)	
4	5.89	3.21	0.208	3.96	38.9	42.2	-0.761	-0.439	0.226
	(0.19)	(0.11)	(0.0025)	(0.27)	(0.87)	(0.66)	(0.19)	(0.20)	
REP181	6.50	4.12	0.255	2.52	33.3	40.2	-0.732	-0.07	0.138
	(0.31)	(0.14)	(0.0025)	(0.14)	(0.69)	(1.05)	(0.10)	(0.13)	
2	7.33	3.13	0.284	2.58	35.2	36.4	-0.622	0.147	0.135
	(0.27)	(0.1)	(0.0036)	(0.95)	(0.75)	(0.84)	(0.09)	(0.11)	
3	7.24	3.34	0.286	2.70	34.7	36.5	-0.856	-0.07	0.134
	(0.33)	(0.11)	(0.0049)	(0.17)	(0.62)	(1.08)	(0.06)	(0.1)	
4	6.89	3.50	0.271	2.32	34.1	39.1	-8.22	-0.114	0.182
	(0.31)	(0.10)	(0.0049)	(0.12)	(0.57)	(1.07)	(0.06)	(0.1)	
REP191	7.73	3.58	0.280	3.48	35.6	41.4	-0.849	-0.225	0.0912
	(0.42)	(0.19)	(0.0031)	(0.26)	(0.58)	(0.84)	(0.08)	(0.12)	
2	7.27	3.52	0.268	2.85	36.4	39.6	-0.785	-0.134	0.137
	(0.49)	(0.21)	(0.0033)	(0.20)	(0.69)	(1.00)	(0.09)	(0.12)	
3	7.04	3.42	0.279	3.23	34.9	37.6	-0.876	-0.15	0.131
	(0.45)	(0.175)	(0.0045)	(0.31)	(0.68)	(1.00)	(0.06)	(0.10)	
4	7.57	4.06	0.281	3.10	34.6	40.4	-0.933	-0.09	0.091
	(0.43)	(0.162)	(0.0063)	(0.26)	(0.46)	(1.11)	(0.05)	(0.09)	

continued .....

E.2 Continued .....

File	$\dot{Q}$	V_A	$\dot{M}$	V_{TC}	$P_{A(0)}$	$P_{TC(0)}$	a	b	$\sum e^2_{i/m}$
REP201	5.87	2.76	0.184	4.54	37.0	42.3	-0.863	-0.267	0.084
	(0.24)	(0.13)	(0.0021)	(0.46)	(0.51)	(0.63)	(0.09)	(0.13)	
2	5.46	2.49	0.171	3.84	38.9	42.1	-0.868	-0.279	0.096
	(0.23)	(0.12)	(0.0021)	(0.42)	(0.56)	(0.68)	(0.08)	(0.12)	
3	5.64	2.49	0.179	3.99	39.0	42.3	-0.871	-0.371	0.068
	(0.18)	(0.11)	(0.0018)	(0.28)	(0.55)	(0.52)	(0.11)	(0.15)	
4	5.52	2.45	0.176	3.79	38.5	41.5	-0.828	-0.319	0.084
	(0.2)	(0.11)	(0.0017)	(0.30)	(0.47)	(0.54)	(0.10)	(0.14)	

APPENDIX F

FORMULA FOR π_1 , π_2 , z and ω for the DFP, RK1 and BFGS FACTORISED QUASI-NEWTON UPDATES.

(i) BFGS UPDATE

$$z^{(k)} = y^{(k)} \qquad \text{(F.1)}$$

$$\omega^{(k)} = g^{(k)} \qquad \text{(F.2)}$$

$$\pi_1 = \frac{1}{\alpha^{(k)} \delta} \qquad \text{(F.3)}$$

$$\pi_2 = \frac{1}{p^{(k)T} g^{(k)}} \qquad \text{(F.4)}$$

(ii) DFP UPDATE

$$z^{(k)} = (\xi\delta - 1)\, g^{(k)} + g^{(k+1)} \qquad \text{(F.5)}$$

$$\omega^{(k)} = g^{(k)} \qquad \text{(F.6)}$$

$$\pi_1 = \frac{1}{\xi\delta 2} \qquad \text{(F.7)}$$

$$\pi_2 = -\xi \qquad \text{(F.8)}$$

(iii) RK1 UPDATE

$$z^{(k)} = g^{(k+1)} + (\alpha^{(k)} - 1)\, g^{(k)} \qquad \text{(F.9)}$$

$$\omega^{(k)} = 0 \qquad \text{(F.10)}$$

$$\pi_1 = \frac{1}{\alpha^{(k)} z^{(k)T} p^{(k)}} \qquad \text{(F.11)}$$

$$\pi_2 = 0 \qquad \text{(F.12)}$$

Note :-

$$\delta = y^{(k)T} p^{(k)} \qquad \text{(F.13)}$$

$$\xi = \frac{\alpha^{(k)}}{g^{(k+1)T} p^{(k)} - (\alpha^{(k)} + 1)\, g^{(k)T} p^{(k)}} \qquad \text{(F.14)}$$

APPENDIX G

```
C
C***  FILE : NLSRUN.FOR  (RT-11  RAB : 26-FEB-79)
C***  RUN MODULE FOR USE WITH NLLS. GOES IN OVERLAY TWO (OVLIB2).
C***  FAST VERSION WHICH USES DOUBLE BUFFERING MACROS TO
C***  SPEED UP I/O.
C
C***  HOMOGENEOUS CO2 GAS TRANSPORT MODEL.
C***  ''RUN'' SUBROUTINE FOR USE WITH GILL-MURRAY NON LINEAR
C***  LEAST SQUARES PROGRAMME.
C***  USES EXPLICIT GRADIENT INFORMATION SO THAT SENSITIVITY
C***  CO-SYSTEM MUST ALSO BE EVALUATED.WORKS WITH FOUR,FIVE,
C***  OR SIX PARAMETER MODEL.
C
      SUBROUTINE RUN(PAR,F,RJ,FX,IU,IV)
C
      DIMENSION PAR(IV),F(IU),RJ(IU,IV),PAR1(6),SENPI(6),SENPA(6),
     1  SSUMVD(6),SUMSEN(6),SMEAN(6),SENPT(6),N1(3,80),N2(3,80)
      COMMON ITER,NOPAR,NPTS
      COMMON /BUFFER/ DBUFF(512)
      COMMON /UNITS/ INN,IOUT
      COMMON /SCLING/ SCPAR(6,2)
      COMMON /BLOCK0/ DELT,TOTSAM,NOBLKS,NOSMRC,NCHSTR
      COMMON /MODEL/ VDM,PAIN,SB,AINT,EVET,NETD(4,250),PABAR,PT0SS.
      REAL MP
      INTEGER TOTSAM,DBUFF
      EQUIVALENCE (N1(1,1),DBUFF(1)),(N2(1,1),DBUFF(257))
      EQUIVALENCE (QDOT,PAR1(1)),(VA,PAR1(2)),(MP,PAR1(3)),
     1  (VT,PAR1(4)),(PA0,PAR1(5)),(PT0,PAR1(6))
C
C***  CONVERT L/M QUANTITIES TO L/S AND GET CORRECT I.C'S FOR
C***  GIVEN MODEL ORDER. UPDATE ITERATION COUNT.
C
      ITER=ITER+1
      CALL DSCLE(PAR,PAR1)
      QDOT=QDOT/60.0
      MP=MP/60.0
      PA0M=PAIN
      IF(NOPAR.EQ.5.OR.NOPAR.EQ.6)PA0M=PA0
      PDIFF=MP/(QDOT*SB)-AINT/SB
      PT0SS=PA0M+PDIFF
      IF(NOPAR.EQ.4)PT0M=PABAR+PDIFF
      IF(NOPAR.EQ.5)PT0M=PA0+PDIFF
      IF(NOPAR.EQ.6)PT0M=PT0
C
C***  WORK OUT I.C'S FOR SENSITIVITY CO-SYSTEM DEPENDING ON
C***  GIVEN MODEL ORDER.
C
      DO 1 I=1,NOPAR
      SENPA(I)=0.0
1     SENPT(I)=0.0
      IF(NOPAR.EQ.6)GOTO 3
      SENPT(3)=1.0/(SB*QDOT)
      SENPT(1)=-1.0*MP*SENPT(3)/QDOT
      IF(NOPAR.EQ.5)GOTO 2
      GOTO 4
2     SENPA(5)=1.0
      GOTO 4
3     SENPA(5)=1.0
```

Appendix G cont'd.....

```
      SENPT(6)=1.0
C
C***  INITIALISE FLAGS, INTERMEDIATE STORAGE AREAS ETC.
C***  READ IN FIRST BUFFER OF DATA.
C
4     CALL TRREAD
      SUMF1=0.0
      SUMMOD=0.0
      DO 5 I=1,NOPAR
      SUMSEN(I)=0.0
      SMEAN(I)=SENPA(I)
5     SSUMVD(I)=0.0
      SUMF2=0.0
      SUMDAT=0.0
      FX=0.0
      SUMVD=0.0
      SUMFVD=0.0
      PAMEAN=PA0M
      NOSAM=0
      NPTS=0
      IBLK=0
      JBR=1
C
C***  NOW READ IN AND OPERATE ON RELAVENT BLOCK OF DATA DEPENDING
C***  ON WHETHER IT IS ODD OR EVEN.
C
10    IBLK=IBLK+1
      CALL TRREAD
      DO 100 I=1,NOSMRC
20    NOSAM=NOSAM+1
      IF(MOD(IBLK,2).NE.0)GOTO 21
      FLOW=FLOAT(N1(1,I))/3000.0
      PCO2=FLOAT(N1(2,I))/400.0
      VOL=FLOAT(N1(3,I))/5000.0
      GOTO 22
21    FLOW=FLOAT(N2(1,I))/3000.0
      PCO2=FLOAT(N2(2,I))/400.0
      VOL=FLOAT(N2(3,I))/5000.0
22    CONTINUE
C
C***  GET CORRECT VA FOR CURRENT TIDAL VOL.
C
      IF(VOL)30,25,30
25    VA0=VA
30    VA=VA0+VOL
C
C***  GET CORRECT INSPIRED PCO2 AND ASSOCIATED SENSITIVITIES
C***  DEPENDING ON PHASE OF BREATH.
C
      DO 26 J=1,NOPAR
26    SENPI(J)=0.0
      IF(VOL.GT.VDM.OR.FLOW.LE.0.0)GOTO 31
      PCO2=PAMEAN
      DO 27 J=1,NOPAR
27    SENPI(J)=SMEAN(J)
C
C***  CALL MODEL SUBROUTINE WHICH UPDATE MODEL AND SENSITIVITY
C***  COSYSTEM USING EULER.
```

```
C
31     CALL MODELL(QDOT,VA,MP,VT,FLOW,FCO2,SENFI,VOL,FA0M,FT0M,
     1   SENFA,SENFT)
C
       IF(NOSAM.LT.NETD(1,JBR))GOTO 40
       IF(NOSAM.GT.NETD(2,JBR))GOTO 32
C
C***   MODEL E/T REGION - UPDATE FLOWS AND FLOW WEIGHTED MEANS.
C
       SUMMOD=SUMMOD+FA0M*FLOW
       DO 41 J=1,NOPAR
41     SUMSEN(J)=SUMSEN(J)+SENFA(J)*FLOW
       SUMF1=SUMF1+FLOW
       GOTO 33
C
C***   LAST DEADSPACE OF EXPIRATION. UPDATE FLOW WEIGHTED MEANS TO
C***   USE AS INPUTS FOR FIRST DEADSPACE OF PRECEDING INSPIRATION.
C
32     SUMVD=SUMVD+FA0M*FLOW
       DO 43 J=1,NOPAR
43     SSUMVD(J)=SSUMVD(J)+SENFA(J)*FLOW
       SUMFVD=SUMFVD+FLOW
C
33     IF(NOSAM.LT.NETD(3,JBR))GOTO 40
34     IF(NOSAM.GT.NETD(4,JBR))GOTO 36
C
C***   DATA E/T REGION - UPDATE FLOW WEIGHTED SENSITIVITIES AND FLOW.
C
       SUMDAT=SUMDAT+FCO2*FLOW
       SUMF2=SUMF2+FLOW
       GOTO 40
C
C***   END OF BREATH. UPDATE PER BREATH INFORMATION (I.E. MEAN
C***   MODEL AND DATA FCO2,ERROR , ASSOCIATED SENSITIVITIES
C***   (NOTE THESE ARE SCALED!!!), AND MEAN FICO2 AND SENSITIVITIES
C***   FOR FIRST BREATH. FINALLY RESET STORES FOR F/W MEANS.
C***   DON'T BOTHER IF BAD BREATH (I.E. VOL < VD).
C
36     IF(SUMF1.EQ.0.0.OR.SUMF2.EQ.0.0)GOTO 38
       NPTS=NPTS+1
       F(NPTS)=SUMMOD/SUMF1-SUMDAT/SUMF2
       FX=FX+F(NPTS)*F(NPTS)
       DO 39 J=1,NOPAR
       RJ(NPTS,J)=SCPAR(J,1)*SUMSEN(J)/SUMF1
       IF(J.EQ.1.OR.J.EQ.3)RJ(NPTS,J)=RJ(NPTS,J)/60.0
39     CONTINUE
38     JBR=JBR+1
       IF(VOL.GT.-VDM)GOTO 46
C
       PAMEAN=SUMVD/SUMFVD
       DO 45 J=1,NOPAR
45     SMEAN(J)=SSUMVD(J)/SUMFVD
46     CONTINUE
       DO 47 J=1,NOPAR
       SSUMVD(J)=0.0
47     SUMSEN(J)=0.0
       SUMF1=0.0
       SUMF2=0.0
```

Appendix G cont'd.....

```
      SUMFVD=0.0
      SUMMOD=0.0
      SUMDAT=0.0
      SUMVD=0.0
C
40    CONTINUE
      IF(NOSAM.EQ.TOTSAM)GOTO 150
100   CONTINUE
      GOTO 10
C
C***  REWIND DATA FILE AND OUTPUT FX TO TERMINAL.
C
150   CALL TRRWND
D      RFX=FX/FLOAT(NPTS)
D      WRITE(IOUT,1000)ITER,RFX
D1000  FORMAT(/1X,' ITER = ',I3,' RFX = ',G15.6)
      RETURN
      END
C
C***  MODEL SUBROUTINE FOR USE WITH ''NLSRUN''.
C***  HOMOGENEOUS CO2 MODEL.
C***  MODEL EQNS AND ASSOCIATED SENSITIVITY COSYSTEM UPDATED
C***  USING EULER.      RAB... 13-FEB-79..
C
      SUBROUTINE MODELL(QDOT,VA,MP,VT,FLOW,PCO2,SENPI,VOL,PA0M,
     1  PT0M,SENPA,SENPT)
C
      DIMENSION SENPI(6),SENPA(6),SENPT(6),DSENPA(6),DSENPT(6)
      COMMON ITER,NOPAR
      COMMON /BLOCK0/ DELT
      COMMON /MODEL/ VDM,PAIN,SB,AINT
      REAL MP
      DATA CONST/863.004/
C
C***  SOLVE MODEL EQNS FIRST.
C
      THING1=QDOT*(SB*(PT0M-PA0M)+AINT)
      THING2=0.0
      IF(FLOW.GT.0.0)THING2=FLOW*(PCO2-PA0M)
      DELTPA=(THING1*CONST+THING2)/VA
      DELTPT=(MP-THING1)/(SB*VT)
      PA0M=PA0M+DELTPA*DELT
      PT0M=PT0M+DELTPT*DELT
C
C***  GENERATION OF SENSITIVITY COSYSTEM.
C***  COMPUTE COUPLING TERMS FIRST.
C
      DSENPA(1)=THING1*CONST/QDOT
      DSENPT(1)=-1.0*THING1/QDOT
      DSENPA(2)=(-1.0*THING1*CONST-THING2)/VA
      DSENPT(2)=0.0
      DSENPA(3)=0.0
      DSENPT(3)=1.0
      DSENPA(4)=0.0
      DSENPT(4)=(THING1-MP)/VT
      IF(NOPAR.EQ.4)GOTO 10
      DSENPA(5)=0.0
      DSENPT(5)=0.0
```

Appendix G cont'd.....

```
      IF( NOPAR.EQ.5 )GOTO 10
      DSENPA( 6 )=0.0
      DSENPT( 6 )=0.0
C
C***  NOW COMPUTE DECOUPLED TERMS.
C***  SOLVE TOTAL SENSITIVITY COSYSTEM BY ADDING IN COUPLING
C***  TERMS CALCULATED ABOVE.
C
10    DO 20 I=1,NOPAR
      THING1=QDOT*SB*( SENPT( I )-SENPA( I ) )
      THING2=0.0
      IF( FLOW.GT.0.0 )THING2=FLOW*( SENPI( I )-SENPA( I ) )
      DSENPA( I )=( DSENPA( I )+THING1*CONST+THING2 )/VA
      DSENPT( I )=( DSENPT( I )-THING1 )/( SB*VT )
      SENPA( I )=SENPA( I )+DSENPA( I )*DELT
20    SENPT( I )=SENPT( I )+DSENPT( I )*DELT
C
      RETURN
      END
```